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#### INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup>:

G01N 33/53

(11) International Publication Number: WO 98/45704

(43) International Publication Date: 15 October 1998 (15.10.98)

(21) International Application Number:

PCT/DK98/00145

(22) International Filing Date:

7 April 1998 (07.04.98)

(30) Priority Data:

0392/97

7 April 1997 (07.04.97)

DK

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

#### Published

Without international search report and to be republished upon receipt of that report.

(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

#### (57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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WO 98/45704 PCT/DK98/00145

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A METHOD for extracting quantitative information relating to an influence on a cellular response

#### FIELD OF INVENTION

The present invention relates to a method and tools for extracting quantitative information relating to an influence, on a cellular response, in particular an influence caused by contacting or incubating the cell with a substance influencing a cellular response, where the cellular response is manifested in redistribution of at least one component in the cell. In particular, the invention relates to a method for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway. The method of the invention may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process, for example in connection with screening for new drugs, testing of substances for toxicity, identifying drug targets for known or novel drugs. Other valuable uses of the method and technology of the invention will be apparent to the skilled person on the basis of the following disclosure. In a particular embodiment of the invention, the present invention relates to a method of detecting intracellular translocation or redistribution of biologically active polypeptides, preferably an enzyme, affecting intracellular processes, and a DNA construct and a cell for use in the method.

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#### BACKGROUND OF THE INVENTION

Intracellular pathways are tightly regulated by a cascade of components that undergo modulation in a temporally and spatially characteristic manner. Several disease states can be attributed to altered activity of individual signalling components (i.e. protein kinases, protein phosphatases, transcription factors). These components therefore render themselves as attractive targets for therapeutic intervention.

Protein kinases and phosphatases are well described components of several intracellular signalling pathways. The catalytic activity of protein kinases and phosphatases are assumed to play a role in virtually all regulatable cellular processes. Although the involvement of protein kinases in cellular signalling and regulation have been subjected to extensive studies, detailed knowledge on e.g. the exact timing and spatial characteristics of signalling events is often difficult to obtain due to lack of a convenient technology.

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Novel ways of monitoring specific modulation of intracellular pathways in intact, living cells is assumed to provide new opportunities in drug discovery, functional genomics, toxicology, patient monitoring etc.

The spatial orchestration of protein kinase activity is likely to be essential for the high degree of specificity of individual protein kinases. The phosphorylation mediated by protein kinases is balanced by phosphatase activity. Also within the family of phosphatases translocation has been observed, e.g. translocation of PTP2C to membrane ruffles [(Cossette *et al.*1996)], and likewise is likely to be indicative of phosphatase activity.

Protein kinases often show a specific intracellular distribution before, during and after activation. Monitoring the translocation processes and/or redistribution of individual protein kinases or subunits thereof is thus likely to be indicative of their functional activity. A connection between translocation and catalytic activation has been shown for protein kinases like the diacyl glycerol (DAG)-dependent protein kinase C (PKC), the cAMP-dependent protein kinase (PKA) [(DeBernardi et al.1996)] and the mitogen-activated-protein kinase Erk-1 [(Sano et al.1995)].

Commonly used methods of detection of intracellular localisation/activity of protein kinases and phosphatases are immunoprecipitation, Western blotting and immunocytochemical detection.

Taking the family of diacyl glycerol (DAG)-dependent protein kinase Cs (PKCs) as an example, it has been shown that individual PKC isoforms that are distributed among different tissues and cells have different activator requirements and undergo differential translocation in response to activation. Catalytically inactive DAG-dependent PKCs are generally distributed throughout the cytoplasm, whereas they upon activation translocate to become associated with different cellular components, e.g. plasma membrane [(Farese, 1992),(Fulop Jr. et al.1995)] nucleus [(Khalil et al.1992)], cytoskeleton [(Blobe et al.1996)]. The translocation phenomenon being indicative of PKC activation has been monitored using different approaches: a) immunocytochemistry where the localisation of individual isoforms can be detected after permeabilisation and fixation of the cells [(Khalil et al.1992)]; and b) tagging all DAG-dependent PKC isoforms with a fluorescently labelled phorbol myristate acetate (PMA) [(Godson et al.1996)]; and c) chemical tagging PKC b1 with the fluorophore Cy3 [(Bastiaens & Jovin 1996)] and d) genetic tagging of PKCα ([Schmidt et al. 1997]) and of PKCγ and PKC ε ([Sakai et al. 1996]). The first method does not provide dynamic information whereas the latter methods will. Tagging PKC with fluorescently labelled phorbol myristate acetate cannot

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distinguish between different DAG-dependent isoforms of PKC but will label and show movement of all isoforms. Chemical and genetic labelling of specific DAG-dependent PKCs confirmed that they in an isoform specific manner upon activation move to cell periphery or nucleus.

In an alternative method, protein kinase A activity has been measured in living cells by chemical labelling one of the kinase's subunit (Adams *et al.*1991). The basis of the methodology is that the regulatory and catalytic subunit of purified protein kinase A is labelled with fluorescein and rhodamine, respectively. At low cAMP levels protein kinase A is assembled in a heterotetrameric form which enables fluorescence resonance energy transfer between the two fluorescent dyes. Activation of protein kinase A leads to dissociation of the complex, thereby eliminating the energy transfer. A disadvantage of this technology is that the labelled protein kinase A has to be microinjected into the cells of interest. This highly invasive technique is cumbersome and not applicable to large scale screening of biologically active substances. A further disadvantage of this technique as compared to the presented invention is that the labelled protein kinase A cannot be inserted into organisms/animals as a transgene.

Recently it was discovered that Green Fluorescent Protein (GFP) expressed in many different cell types, including mammalian cells, became highly fluorescent [(Chalfie et al. 1994)]. WO95/07463 describes a cell capable of expressing GFP and a method for detecting a protein of interest in a cell based on introducing into a cell a DNA molecule having DNA sequence encoding the protein of interest linked to DNA sequence encoding a GFP such that the protein produced by the DNA molecule will have the protein of interest fused to the GFP, then culturing the cells in conditions permitting expression of the fused protein and detecting the location of the fluorescence in the cell, thereby localizing the protein of interest in the cell. However, examples of such fused proteins are not provided, and the use of fusion proteins with GFP for detection or quantitation of translocation or redistribution of biologically active polypeptides affecting intracellular processes upon activation, such as proteins involved in signalling pathways, e.g. protein kinases or phosphatases, has not been suggested. WO 95/07463 further describes cells useful for the detection of molecules, such as hormones or heavy metals, in a biological sample, by operatively linking a regulatory element of the gene which is affected by the molecule of interest to a GFP, the presence of the molecules will affect the regulatory element which in turn will affect the expression of the GFP. In this way the gene encoding GFP is used as a reporter gene in a cell which is constructed for monitoring the presence of a specific molecular identity.

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Green Fluorescent Protein has been used in an assay for the detection of translocation of the glucocorticoid receptor (GR) [Carey, KL et al., The Journal of Cell Biology, Vol. 133, No. 5, p. 985-996 (1996)]. A GR-S65TGFP fusion has been used to study the mechanisms involved in translocation of the glucocorticoid receptor (GR) in response to the agonist dexamethasone from the cytosol, where it is present in the absence of a ligand, through the nuclear pore to the nucleus where it remains after ligand binding. The use of a GR-GFP fusion enables real-time imaging and quantitation of nuclear/cytoplasmic ratios of the fluorescence signal.

Many currently used screening programmes designed to find compounds that affect protein kinase activity are based on measurements of kinase phosphorylation of artificial or natural substrates, receptor binding and/or reporter gene expression.

#### DISCLOSURE OF THE INVENTION

The present invention provides an important new dimension in the investigation of cellular systems involving redistribution in that the invention provides quantification of the redistribution responses or events caused by an influence, typically contact with a chemical substance or mixture of chemical substances, but also changes in the physical environment. The quantification makes it possible to set up meaningful relationships, expressed numerically, or as curves or graphs, between the influences (or the degree of influences) on cellular systems and the redistribution response. This is highly advantageous because, as has been found, the quantification can be achieved in both a fast and reproducible manner, and - what is perhaps even more important - the systems which become quantifiable utilizing the method of the invention are systems from which enormous amounts of new information and insight can be derived.

The present screening assays have the distinct advantage over other screening assays, e.g., receptor binding assays, enzymatic assays, and reporter gene assays, in providing a system in which biologically active substances with completely novel modes of action, e.g. inhibition or promotion of redistribution/translocation of a biologically active polypeptide as a way of regulating its action rather than inhibition/activation of enzymatic activity, can be identified in a way that insures very high selectivity to the particular isoform of the biologically active polypeptide and further development of compound selectivity versus other isoforms of

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the same biologically active polypeptide or other components of the same signalling pathway.

In its broadest aspect, the invention relates to a method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, detecting and recording the spatially distributed light from the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution or change in the spatial distribution to the degree of the influence. In a preferred embodiment of the invention the luminophore, which is present in the cell or cells, is capable of being redistributed by modulation of an intracellular pathway, in a manner which is related to the redistribution of at least one component of the intracellular pathway. In another preferred embodiment of the invention, the luminophore is a fluorophore.

#### The cells

In the invention the cell and/or cells are mechanically intact and alive throughout the experiment. In another embodiment of the invention, the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.

The mechanically intact living cell or cells could be selected from the group consisting of fungal cell or cells, such as a yeast cell or cells; invertebrate cell or cells including insect cell or cells; and vertebrate cell or cells, such as mammalian cell or cells. This cell or these cells is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C during the time period over which the influence is observed. In one aspect of the invention the mechanically intact living cell is part of a matrix of identical or non-identical cells.

A cell used in the present invention should contain a nucleic acid construct encoding a fusion polypeptide as defined herein and be capable of expressing the sequence encoded by the construct. The cell is a eukaryotic cell selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; vertebrate cells such as mammalian cells. The preferred cells are mammalian cells.

In another aspect of the invention the cells could be from an organism carrying in at least one of its component cells a nucleic acid sequence encoding a fusion polypeptide as defined herein and be capable of expressing said nucleic acid sequence. The organism is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

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#### The luminophore

The luminophore is the component which allows the redistribution to be visualised and/or recorded by emitting light in a spatial distribution related to the degree of influence. In one embodiment of the invention, the luminophore is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore is capable of associating with a component which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore correlation between the redistribution of the luminophore and the degree of the influence could be determined experimentally. In a preferred aspect of the invention, the luminophore is capable of being redistributed in substantially the same manner as the at least one component of an intracellular pathway. In yet another embodiment of the invention, the luminophore is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a change in the intensity of the luminescence.

The luminophore could be a fluorophore. In a preferred embodiment of the invention, the luminophore could be a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells. The luminophore could be a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.

The luminescent polypeptide could be a GFP as defined herein or could be selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein

such as F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP. The GFP could be N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or a part or a subunit thereof. The fluorescent probe could be a component of a intracellular signalling pathway. The probe is coded for by a nucleic acid construct.

The pathway of investigation in the present invention could be an intracellular signalling pathway.

#### The influence

In a preferred embodiment of the invention, the influence could be contact between the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance. The influence will modulate the intracellular processes. In one aspect the modulation could be an activation of the intracellular processes. In another aspect the modulation could be an deactivation of the intracellular processes. In yet another aspect, the influence could inhibit or promote the redistribution without directly affecting the metabolic activity of the component of the intracellular processes.

In one embodiment the invention is used as a basis for a screening program, where the effect of unknown influences such as a compound library, can be compared to influence of known reference compounds under standardised conditions.

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#### The recording

In addition to the intensity, there are several parameters of fluorescence or luminescence which can be modulated by the effect of the influence on the underlying cellular phenomena, and can therefore be used in the invention. Some examples are resonance energy transfer, fluorescence lifetime, polarisation, wavelength shift. Each of these methods requires a particular kind of filter in the emission light path to select the component of the light desired and reject other components. The recording of property of light could be in the form of an ordered array of values such as a CCD array or a vacuum tube device such as a vidicon tube.

In one embodiment of the invention, the spatially distributed light emitted by a luminophore could be detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of

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which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway. In this embodiment, either the luminophore or the luminescent entity capable of delivering energy to the luminophore undergoes redistribution in response to an influence. The resonance energy transfer would be measured as a change in the intensity of emission from the luminophore, preferably sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion.

In one embodiment of the invention, the recording of the spatially distributed light could be made at a single point in time after the application of the influence. In another embodiment, the recording could be made at two points in time, one point being before, and the other point being after the application of the influence. The result or variation is determined from the change in fluorescence compared to the fluorescence measured prior to the influence or modulation. In another embodiment of the invention, the recording could be performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes. The result or variation is determined from the change in fluorescence over time. The result or variation could also be determined as a change in the spatial distribution of the fluorescence over time.

#### **Apparatus**

The recording of spatially distributed luminescence emitted from the luminophore is performed by an apparatus for measuring the distribution of fluorescence in the cell or cells, and thereby any change in the distribution of fluorescence in the cell or cells, which includes at a minimum the following component parts: (a) a light source, (b) a method for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a device which can rapidly block or pass the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence emission, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to

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record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

In a preferred embodiment of the invention the apparatus system is automated. In one embodiment the components in d and e mentioned above comprise a fluorescence microscope. In one embodiment the component in f mentioned above is a CCD camera.

In one embodiment the image is formed and recorded by an optical scanning system.

In one embodiment a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance. Preferably, the liquid addition system is under the control of the computer or electronic system. Such an automated system can be used for a screening program due to its ability to generate results from a larger number of test compounds than a human operator could generate using the apparatus in a manual fashion.

#### Quantitation of the influence

The recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures. The quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence. This calibration procedure is developed according to principles described below (Developing an Image-based Assay Technique). Specific descriptions of the procedures for particular assays are given in the examples.

While the stepwise procedure necessary to reduce the image or images to the value representative of the is particular to each assay, the individual steps are generally well-known methods of image processing. Some examples of the individual steps are point operations such as subtraction, ratioing, and thresholding, digital filtering methods such as smoothing, sharpening, and edge detection, spatial frequency methods such as Fourier filtering, image cross-correlation and image autocorrelation, object finding and classification (blob analysis),

and colour space manipulations for visualisation. In addition to the algorithmic procedures, heuristic methods such as neural networks may also be used.

#### Nucleic acid constructs

- The nucleic acid constructs used in the present invention encode in their nucleic acid sequences fusion polypeptides comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, preferably an F64L mutant of GFP, N- or C-terminally fused, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a phosphatase.
  - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a transcription factor or a part thereof which changes cellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
  - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a part thereof which changes cellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation. In a preferred embodiment the biologically active polypeptide encoded by the nucleic acid construct is a PKAc-F64L-S65T-GFP fusion.

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In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a mitogen-activated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation. In preferred embodiments the biologically active polypeptide encoded by the nucleic acid constructs are an ERK1-F64L-S65T-GFP fusion or an EGFP-ERK1 fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cyclin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.

In one preferred embodiment of the invention the nucleic acid constructs may be DNA constructs.

- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct In one embodiment the gene encoding GFP in the nucleic acid construct is derived from Aequorea victoria. In a preferred embodiment the gene encoding GFP in the nucleic acid construct is EGFP or a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.
- In preferred embodiments of the invention the DNA constructs which can be identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142 or are variants of these sequences capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, e.g. an isoform, or a splice variant or a homologue from another species.

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## Screening program

The present invention describes a method that may be used to establish a screening program for the identification of biologically active substances that directly or indirectly affects intracellular signalling pathways and because of this property are potentially useful as medicaments. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biological activity.

In one embodiment of the invention the screening program is used for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biologically toxic activity. In one embodiment of a screening program a compound that modulates a component of an intracellular pathway as defined herein, can be found and the therapeutic amount of the compound estimated by a method according to the method of the invention. In a preferred embodiment the present invention leads to the discovery of a new way of treating a condition or disease related to the intracellular function of a biologically active polypeptide comprising administration to a patient suffering from said condition or disease of an effective amount of a compound which has been discovered by any method according to the invention. In another preferred embodiment of the invention a method is established for identification of a new drug target or several new drug targets among the group of biologically active polypeptides which are components of intracellular signalling pathways.

In another embodiment of the invention an individual treatment regimen is established for the selective treatment of a selected patient suffering from an ailment where the available medicaments used for treatment of the ailment are tested on a relevant primary cell or cells obtained from said patient from one or several tissues, using a method comprising transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, transferring the transfected cell or cells back the said patient, or culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of the available medicaments, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to

detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting one or more medicament or medicaments based on the desired activity and acceptable level of side effects and administering an effective amount of these medicaments to the selected patient.

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## Back-tracking of a signal transduction pathway

The present invention describes a method that may be used to establish a screening program for back-tracking signal transduction pathways as defined herein. In one embodiment the screening program is used to establish more precisely at which level one or several compounds affect a specific signal transduction pathway by successively or in parallel testing the influence of the compound or compounds on the redistribution of spatially resolved luminescence from several of the luminophores which undergo a change in distribution upon activation or deactivation of the intracellular signalling pathway under study.

## 15 Construction and testing of probes

In general, a probe, i.e. a "GeneX"-GFP fusion or a GFP-"GeneX" fusion, is constructed using PCR with "GeneX"-specific primers followed by a cloning step to fuse "GeneX" in frame with GFP. The fusion may contain a short vector derived sequence between "GeneX" and GFP (e.g. part of a multiple cloning site region in the plasmid) resulting in a peptide linker between "GeneX" and GFP in the resulting fusion protein.

#### Detailed stepwise procedure:

- Identifying the sequence of the gene. This is most readily done by searching a depository of genetic information, e.g. the GenBank Sequence Database, which is widely available and routinely used by molecular biologists. In the specific examples below the GenBank Accession number of the gene in question is provided.
- Design of gene-specific primers. Inspection of the sequence of the gene allows design of gene-specific primers to be used in a PCR reaction. Typically, the top-strand primer encompasses the ATG start codon of the gene and the following ca. 20 nucleotides, while the bottom-strand primer encompasses the stop codon and the ca. 20 preceding nucleotides, if

the gene is to be fused behind GFP, i.e. a GFP-"GeneX" fusion. If the gene is to be fused in front of GFP, i.e. a "GeneX"-GFP fusion, a stop codon must be avoided. Optionally, the full length sequence of GeneX may not be used in the fusion, but merely the part which localizes and redistributes like GeneX in response to a signal.

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In addition to gene-specific sequences, the primers contain at least one recognition sequence for a restriction enzyme, to allow subsequent cloning of the PCR product. The sites are chosen so that they are unique in the PCR product and compatible with sites in the cloning vector. Furthermore, it may be necessary to include an exact number of nucleotides between the restriction enzyme site and the gene-specific sequence in order to establish the correct reading frame of the fusion gene and/or a translation initiation consensus sequence. Lastly, the primers always contain a few nucleotides in front of the restriction enzyme site to allow efficient digestion with the enzyme.

- -Identifying a source of the gene to be amplified. In order for a PCR reaction to produce a product with gene-specific primers, the gene-sequence must initially be present in the reaction, e.g. in the form of cDNA. Information in GenBank or the scientific literature will usually indicate in which tissue(s) the gene is expressed, and cDNA libraries from a great variety of tissues or cell types from various species are commercially available, e.g. from Clontech
   (Palo Alto), Stratagene (La Jolla) and Invitrogen (San Diego). Many genes are also available in cloned form from The American Type Tissue Collection (Virginia).
  - Optimizing the PCR reaction. Several factors are known to influence the efficiency and specificity of a PCR reaction, including the annealing temperature of the primers, the concentration of ions, notably Mg²⁺ and K⁺, present in the reaction, as well as pH of the reaction. If the result of a PCR reaction is deemed unsatisfactory, it might be because the parameters mentioned above are not optimal. Various annealing temperatures should be tested, e.g. in a PCR machine with a built-in temperature gradient, available from e.g. Stratagene (La Jolla), and/or various buffer compositions should be tried, e.g. the OptiPrime buffer system from Stratagene (La Jolla).

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WO 98/45704 PCT/DK98/00145

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- Cloning the PCR product. The vector into which the amplified gene product will be cloned and fused with GFP will already have been taken into consideration when the primers were designed. When choosing a vector, one should at least consider in which cell types the probe subsequently will be expressed, so that the promoter controlling expression of the probe is compatible with the cells. Most expression vectors also contain one or more selective markers, e.g. conferring resistance to a drug, which is a useful feature when one wants to make stable transfectants. The selective marker should also be compatible with the cells to be used.

The actual cloning of the PCR product should present no difficulty as it typically will be a one-step cloning of a fragment digested with two different restriction enzymes into a vector digested with the same two enzymes. If the cloning proves to be problematic, it may be because the restriction enzymes did not work well with the PCR fragment. In this case one could add longer extensions to the end of the primers to overcome a possible difficulty of digestion close to a fragment end, or one could introduce an intermediate cloning step not based on restriction enzyme digestion. Several companies offer systems for this approach, e.g. Invitrogen (San Diego) and Clontech (Palo Alto).

Once the gene has been cloned and, in the process, fused with the GFP gene, the resulting product, usually a plasmid, should be carefully checked to make sure it is as expected. The most exact test would be to obtain the nucleotide sequence of the fusion-gene.

### Testing the probe

Once a DNA construct for a probe has been generated, its functionality and usefulness may be tested by subjecting it to the following tests:

- Transfecting it into cells capable of expressing the probe. The fluorescence of the cell is inspected soon after, typically the next day. At this point, two features of cellular fluorescence are noted: the intensity and the sub-cellular localization.

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The intensity should usually be at least as strong as that of unfused GFP in the cells. If it is not, the sequence or quality of the probe-DNA might be faulty, and should be carefully checked.

The sub-cellular localization is an indication of whether the probe is likely to perform well. If it 5 localizes as expected for the gene in question, e.g. is excluded from the nucleus, it can immediately go on to a functional test. If the probe is not localized soon after the transfection procedure, it may be because of overexpression at this point in time, as the cell typically will have taken of very many copies of the plasmid, and localization will occur in time, e.g. within a few weeks, as plasmid copy number and expression level decreases. If localization does 10 not occur after prolonged time, it may be because the fusion to GFP has destroyed a localization function, e.g. masked a protein sequence essential for interaction with its normal cellular anchor-protein. In this case the opposite fusion might work, e.g. if GeneX-GFP does not work, GFP-GeneX might, as two different parts of GeneX will be affected by the proximity to GFP. If this does not work, the proximity of GFP at either end might be a problem, and it 15 could be attempted to increase the distance by incorporating a longer linker between GeneX and GFP in the DNA construct.

If there is no prior knowledge of localization, and no localization is observed, it may be because the probe should not be localized at this point, because such is the nature of the protein fused to GFP. It should then be subjected to a functional test.

In a functional test, the cells expressing the probe are treated with at least one compound known to perturb, usually by activating, the signalling pathway on which the probe is expected to report by redistributing itself within the cell. If the redistribution is as expected, e.g. if prior knowledge tell that it should translocate from location X to location Y, it has passed the first critical test. In this case it can go on to further characterization and quantification of the response.

If it does not perform as expected, it may be because the cell lacks at least one component of the signalling pathway, e.g. a cell surface receptor, or there is species incompatibility, e.g. if the probe is modelled on sequence information of a human geneproduct, and the cell is of hamster origin. In both instances one should identify other cell types for the testing process where these potential problems would not apply.

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If there is no prior knowledge about the pattern of redistribution, the analysis of the redistribution will have to be done in greater depth to identify what the essential and indicative features are, and when this is clear, it can go on to further characterization and quantification of the response. If no feature of redistribution can be identified, the problem might be as mentioned above, and the probe should be retested under more optimal cellular conditions.

If the probe does not perform under optimal cellular conditions it's back to the drawing board.

## Developing an image-based assay technique

The process of developing an image-based redistribution assay begins with either the unplanned experimental observation that a redistribution phenomenon can be visualised, or the design of a probe specifically to follow a redistribution phenomenon already known to occur. In either event, the first and best exploratory technique is for a trained scientist or technician to observe the phenomenon. Even with the rapid advances in computing technology, the human eye-brain combination is still the most powerful pattern recognition system known, and requires no advance knowledge of the system in order to detect potentially interesting and useful patterns in raw data. This is especially if those data are presented in the form of images, which are the natural "data type" for human visual processing. Because human visual processing operates most effectively in a relatively narrow frequency range, i.e., we cannot see either very fast or very slow changes in our visual field, it may be necessary to record the data and play it back with either time dilation or time compression.

Some luminescence phenomena cannot be seen directly by the human eye. Examples include polarization and fluorescence lifetime. However, with suitable filters or detectors, these signals can be recorded as images or sequences of images and displayed to the human in the fashion just described. In this way, patterns can be detected and the same methods can be applied.

Once the redistribition has been determined to be a reproducible phenomenon, one or more data sets are generated for the purpose of developing a procedure for extracting the quantitative information from the data. In parallel, the biological and optical conditions are determined which will give the best quality raw data for the assay. This can become an iterative process; it may be necessary to develop a quantitative procedure in order to assess the effect on the assay of manipulating the assay conditions.

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The data sets are examined by a person or persons with knowledge of the biological phenomenon and skill in the application of image processing techniques. The goal of this exercise is to determine or at least propose a method which will reduce the image or sequence of images constituting the record of a "response" to a value corresponding to the degree of the response. Using either interactive image processing software or an image processing toolbox and a programming language, the method is encoded as a procedure or algorithm which takes the image or images as input and generates the degree of response (in any units) as its output. Some of the criteria for evaluating the validity of a particular procedure are:

- Does the degree of the response vary in a biologically significant fashion, i.e., does it show the known or putative dependence on the concentration of the stimulating agent or condition?
- Is the degree of response reproducible, i.e., does the same concentration or level of stimulating agent or condition give the same response with an acceptable variance?
- Is the dynamic range of the response sufficient for the purpose of the assay? If not,
   can a change in the procedure or one of its parameters improve the dynamic range?
- Does the procedure exhibit any clear "pathologies", i.e., does it give ridiculous values for the response if there are commonly occurring imperfections in the imaging process? Can these pathologies be eliminated, controlled, or accounted for?
- Can the procedure deal with the normal variation in the number and/or size of cells in an image?

In some cases the method may be obvious; in others, a number of possible procedures may suggest themselves. Even if one method appears clearly superior to others, optimisation of parameters may be required. The various procedures are applied to the data set and the criteria suggested above are determined, or the single procedure is applied repeatedly with adjustment of the parameter or parameters until the most satisfactory combination of signal, noise, range, etc. are arrived at. This is equivalent to the calibration of any type of single-channel sensor.

The number of ways of extracting a single value from an image are extremely large, and thus an intelligent approach must be taken to the initial step of reducing this number to a small, finite number of possible procedures. This is not to say that the procedure arrived at is

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necessarily the best procedure - but a global search for the best procedure is simply out of the question due to the sheer number of possibilities involved.

Image-based assays are no different than other assay techniques in that their usefulness is characterised by parameters such as the specificity for the desired component of the sample, the dynamic range, the variance, the sensitivity, the concentration range over which the assay will work, and other such parameters. While it is not necessary to characterise each and every one of these before using the assay, they represent the only way to compare one assay with another.

## 10 Example: Developing a Quantitative assay for GLUT4 Translocation

GLUT4 is a member of the class of glucose transporter molecules which are important in cellular glucose uptake. It is known to translocate to the plasma membrane under some conditions of stimulation of glucose uptake. The ability to visualize the glucose uptake response noninvasively, without actually measuring glucose uptake, would be a very useful assay for anyone looking for, for example, treatments for type II diabetes.

A CHO cell line which stably expressed the human insulin receptor was used as the basis for a new cell line which stably expressed a fusion between GLUT4 and GFP. This cell line was expected to show translocation of GLUT4 to the plasma membrane as visualized by the movement of the GFP. The translocation could definitely be seen in the form of the appearance of local increases in the fluorescence in regions of the plasma membrane which had a characteristic shape or pattern. This is shown in Figure 12.

These objects became known as "snircles", and the phenomenon of their appearance as "snircling". In order to quantitate their appearance, a method had to be found to isolate them as objects in the image field, and then enumerate them, measure their area, or determine some parameter about them which correlated in a dose-dependent fashion with the concentration of insulin to which the cells had been exposed. In order to separate the snircles, a binarization procedure was applied in which one copy of the image smoothed with a relatively severe gaussian kernel (sigma = 2.5) was subtracted from another copy to which only a relatively light gaussian smooth had been applied (sigma=0.5). The resultant image was rescaled to its min/max range, and an automatic threshold was applied to divide the image into two levels. The thresholded image contains a background of one value all found object with another value. The found objects were first filtered through a filter to remove objects far too

large and far too small to be snircles. The remaining objects, which represent snircles and other artifacts from the image with approximately the same size and intensity characteristics as snircles, are passed into a classification procedure which has been previously trained with many images of snircles to recognize snircles and exclude the other artifacts. The result of this procedure is a binary image which shows only the found snircles to the degree to which the classification procedure can accurately identify them. The total area of the snircles is then summed and this value is the quantitative measure of the degree of snircling for that image.

#### 10 Definitions:

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In the present specification and claims, the term "an influence" covers any influence to which the cellular response comprises a redistribution. Thus, e.g., heating, cooling, high pressure, low pressure, humidifying, or drying are influences on the cellular response on which the resulting redistribution can be quantified, but as mentioned above, perhaps the most important influences are the influences of contacting or incubating the cell or cells with substances which are known or suspected to exert and influence on the cellular response involving a redistribution contribution. In another embodiment of the invention the influence could be substances from a compound drug library.

In the present context, the term "green fluorescent protein" is intended to indicate a protein which, when expressed by a cell, emits fluorescence upon exposure to light of the correct excitation wavelength (cf. [(Chalfie et al.1994)]). In the following, GFP in which one or more amino acids have been substituted, inserted or deleted is most often termed "modified GFP". "GFP" as used herein includes wild-type GFP derived from the jelly fish Aequorea victoria and modifications of GFP, such as the blue fluorescent variant of GFP disclosed by Heim et al. (1994). Proc.Natl.Acad.Sci. 91:12501, and other modifications that change the spectral properties of the GFP fluorescence, or modifications that exhibit increased fluorescence when expressed in cells at a temperature above about 30°C described in PCT/DK96/00051, published as WO 97/11094 on 27 March 1997 and hereby incorporated by reference, and which comprises a fluorescent protein derived from Aequorea Green Fluorescent Protein (GFP) or any functional analogue thereof, wherein the amino acid in position 1 upstream from the chromophore has been mutated to provide an increase of fluorescence intensity when the

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fluorescent protein of the invention is expressed in cells. Preferred GFP variants are F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP. An especially preferred variant of GFP for use in all the aspects of this invention is EGFP (DNA encoding EGFP which is a F64L-S65T variant with codons optimized for expression in mammalian cells is available from Clontech, Palo Alto, plasmids containing the EGFP DNA sequence, cf. GenBank Acc. Nos. U55762, U55763).

The term "intracellular signalling pathway" and "signal transduction pathway" are intended to indicate the coordinated intracellular processes whereby a living cell transduce an external or internal signal into cellular responses. Said signal transduction will involve an enzymatic reaction said enzymes include but are not limited to protein kinases, GTPases, ATPases, protein phosphatases, phospholipases. The cellular responses include but are not limited to gene transcription, secretion, proliferation, mechanical activity, metabolic activity, cell death.

The term "second messenger" is used to indicate a low molecular weight component involved in the early events of intracellular signal transduction pathways.

The term "luminophore" is used to indicate a chemical substance which has the property of emitting light either inherently or upon stimulation with chemical or physical means. This includes but is not limited to fluorescence, bioluminescence, phosphorescence, chemiluminescence.

The term "mechanically intact living cell" is used to indicate a cell which is considered living according to standard criteria for that particular type of cell such as maintenance of normal membrane potential, energy metabolism, proliferative capability, and has not experienced any physically invasive treatment designed to introduce external substances into the cell such as microinjection.

The term "physiologically relevant" ,when applied to an experimentally determined redistribution of an intracellular component, as measured by a change in the luminescence properties or distribution, is used to indicate that said redistribution can be explained in terms of the underlying biological phenomenon which gives rise to the redistribution.

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Th terms "image processing" and "image analysis" are used to describe a large family of digital data analysis techniques or combination of such techniques which reduce ordered arrays of numbers (images) to quantitative information describing those ordered arrays of numbers. When said ordered arrays of numbers represent measured values from a physical process, the quantitative information derived is therefore a measure of the physical process.

The term "fluorescent probe" is used to indicate a fluorescent fusion polypeptide comprising a GFP or any functional part thereof which is N- or C-terminally fused to a biologically active polypeptide as defined herein, optionally via a peptide linker consisting of one or more amino acid residues, where the size of the linker peptide in itself is not critical as long as the desired functionality of the fluorescent probe is maintained. A fluorescent probe according to the invention is expressed in a cell and basically mimics the physiological behaviour of the biologically active polypeptide moiety of the fusion polypeptide.

The term "mammalian cell" is intended to indicate any living cell of mammalian origin. The cell may be an established cell line, many of which are available from The American Type Culture Collection (ATCC, Virginia, USA) or a primary cell with a limited life span derived from a mammalian tissue, including tissues derived from a transgenic animal, or a newly established immortal cell line derived froma mammalian tissue including transgenic tissues, or a hybrid cell or cell line derived by fusing different celltypes of mammalian origin e.g. hybridoma cell lines. The cells may optionally express one or more non-native gene products, e.g. receptors, enzymes, enzyme substrates, prior to or in addition to the fluorescent probe. Preferred cell lines include but are not limited to those of fibroblast origin, e.g. BHK, CHO, BALB, or of endothelial origin, e.g. HUVEC, BAE (bovine artery endothelial), CPAE (cow pulmonary artery endothelial) or of pancreatic origin, e.g. RIN, INS-1, MIN6, bTC3, aTC6, bTC6, HIT, or of hematopoietic origin, e.g. adipocyte origin, e.g. 3T3-L1, neuronal/neuroendocrine origin, e.g. AtT20, PC12, GH3, muscle origin, e.g. SKMC, A10, C2C12, renal origin, e.g. HEK 293, LLC-PK1.

The term "hybrid polypeptide" is intended to indicate a polypeptide which is a fusion of at least a portion of each of two proteins, in this case at least a portion of the green fluorescent protein, and at least a portion of a catalytic and/or regulatory domain of a protein kinase. Furthermore a hybrid polypeptide is intended to indicate a fusion polypeptide comprising a

GFP or at least a portion of the green fluorescent protein that contains a functional fluorophore, and at least a portion of a biologically active polypeptide as defined herein provided that said fusion is not the PKC $\alpha$ -GFP, PKC $\gamma$ -GFP, and PKC $\epsilon$ -GFP disclosed by Schmidt et al.and Sakai et al., respectively. Thus, GFP may be N- or C-terminally tagged to a biologically active polypeptide, optionally via a linker portion or linker peptide consisting of a sequence of one or more amino acids. The hybrid polypeptide or fusion polypeptide may act as a fluorescent probe in intact living cells carrying a DNA sequence encoding the hybrid polypeptide under conditions permitting expression of said hybrid polypeptide.

The term "kinase" is intended to indicate an enzyme that is capable of phosphorylating a cellular component.

The term "protein kinase" is intended to indicate an enzyme that is capable of phosphorylating serine and/or threonine and/or tyrosine in peptides and/or proteins.

The term "phosphatase" is intended to indicate an enzyme that is capable of dephosphorylating phosphoserine and/or phosphothreonine and/or phosphotyrosine in peptides and/or proteins.

In the present context, the term "biologically active polypeptide" is intended to indicate a polypeptide affecting intracellular processes upon activation, such as an enzyme which is active in intracellular processes or a portion thereof comprising a desired amino acid sequence which has a biological function or exerts a biological effect in a cellular system. In the polypeptide one or several aminoacids may have been deleted, inserted or replaced to alter its biological function, e.g. by rendering a catalytic site inactive. Preferably, the biologically active polypeptide is selected from the group consisting of proteins taking part in an intracellular signalling pathway, such as enzymes involved in the intracellular phosphorylation and dephosphorylation processes including kinases, protein kinases and phosphorylases as defined herein, but also proteins making up the cytoskeleton play important roles in intracellular signal transduction and are therefore included in the meaning of "biologically active polypeptide" herein. More preferably, the biologically active polypeptide is a protein which according to its state as activated or non-activated changes localisation within the cell, preferably as an in-

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termediary component in a signal transduction pathway. Included in this preferred group of biologically active polypeptides are cAMP dependent protein kinase A.

The term "a substance having biological activity" is intended to indicate any sample which has a biological function or exerts a biological effect in a cellular system. The sample may be a sample of a biological material such as a sample of a body fluid including blood, plasma, saliva, milk, urine, or a microbial or plant extract, an environmental sample containing pollutants including heavy metals or toxins, or it may be a sample containing a compound or mixture of compounds prepared by organic synthesis or genetic techniques.

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The phrase "any change in fluorescence" means any change in absorption properties, such as wavelength and intensity, or any change in spectral properties of the emitted light, such as a change of wavelength, fluorescence lifetime, intensity or polarisation, or any change in the intracellular localisation of the fluorophore. It may thus be localised to a specific cellular component (e.g. organelle, membrane, cytoskeleton, molecular structure) or it may be evenly distributed throughout the cell or parts of the cell.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate.

The term "organism" as used herein indicates any unicellular or multicellular organism preferably originating from the animal kingdom including protozoans, but also organisms that are members of the plant kingdoms, such as algae, fungi, bryophytes, and vascular plants are included in this definition.

The term "nucleic acid" is intended to indicate any type of poly- or oligonucleic acid sequence, such as a DNA sequence, a cDNA sequence, or an RNA sequence.

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The term "biologically equivalent" as it relates to proteins is intended to mean that a first protein is equivalent to a second protein if the cellular functions of the two proteins may substitute for each other, e.g. if the two proteins are closely related isoforms encoded by different genes, if they are splicing variants, or allelic variants derived from the same gene, if they perform identical cellular functions in different cell types, or in different species. The term "biologically equivalent" as it relates to DNA is intended to mean that a first DNA sequ-

ence encoding a polypeptide is equivalent to a second DNA sequence encoding a polypeptide if the functional proteins encoded by the two genes are biologically equivalent.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate a process for defining more precisely at what level a signal transduction pathway is affected, either by the influence of chemical compounds or a disease state in an organism. Consider a specific signal transduction pathway represented by the bioactive polypeptides A - B - C - D, with signal transduction from A towards D. When investigating all components of this signal transduction pathway compounds or disease states that influence the activity or redistribution of only D can be considered to act on C or downstream of C whereas compounds or disease states that influence the activity or redistribution of C and D, but not of A and B can be considered to act downstream of B.

The term "fixed cells" is used to mean cells treated with a cytological fixative such as glutaraldehyde or formaldehyde, treatments which serve to chemically cross-link and stabilize soluble and insoluble proteins within the structure of the cell. Once in this state, such proteins cannot be lost from the structure of the now-dead cell.

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## **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1. CHO cells expressing the PKAc-F64L-S65T-GFP hybrid protein have been treated in HAM's F12 medium with 50 mM forskolin at 37°C. The images of the GFP fluorescence in these cells have been taken at different time intervals after treatment, which were: a) 40 seconds b) 60 seconds c) 70 seconds d) 80 seconds. The fluorescence changes from a punctate to a more even distribution within the (non-nuclear) cytoplasm.

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Figure 2. Time-lapse analysis of forskolin induced PKAc-F64L-S65T-GFP redistribution. CHO cells, expressing the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy. Fluorescence micrographs were acquired at regular intervals from 2 min before to 8 min after the addition of agonist. The cells were challenged with 1 mM forskolin immediately after the upper left image was acquired (t=0). Frames were collected at the following times: i) 0, ii) 1, iii) 2, iv) 3, v) 4 and vi) 5 minutes. Scale bar 10 mm.

Figure 3. Time-lapse analyses of PKAc-F64L-S65T-GFP redistribution in response to various agonists. The effects of 1 mM forskolin (A), 50 mM forskolin (B), 1mM dbcAMP (C) and 100 mM IBMX (D) (additions indicated by open arrows) on the localisation of the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy of CHO/PKAc-F64L-S65T-GFP cells. The effect of addition of 10 mM forskolin (open arrow), followed shortly by repeated washing with buffer (solid arrow), on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed in the same cells (E). In a parallel experiment, the effect of adding 10 mM forskolin and 100 mM IBMX (open arrow) followed by repeated washing with buffer containing 100 mM IBMX (solid arrow) was analysed (F). Removing forskolin caused PKAc-F64L-S65T-GFP fusion protein to return to the cytoplasmic aggregates while this is prevented by the continued presence of IBMX (F). The effect of 100 nM glucagon (Fig 3G, open arrow) on the localisation of the PKAc-F64L-S65T-GFP fusion protein is also shown for BHK/GR, PKAc-F64L-S65T-GFP cells. The effect of 10 mM norepinephrine (H), solid arrow, on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed similarly, in transiently transfected CHO, PKAc-F64L-S65T-GFP cells, pretreated with 10 mM forskolin, open arrow, to increase [cAMP]i. N.B. in Fig 3H the x-axis counts the image numbers, with 12 seconds between images. The raw data of each experiment consisted of 60 fluorescence micrographs acquired at regular intervals including several images acquired before the addition of buffer or agonist. The charts (A-G) each show a quantification of the response seen through all the 60 images, performed as described in analysis method 2. The change in total area of the highly fluorescent aggregates, relative to the initial area of fluorescent aggregates is plotted as the ordinate in all graphs in Figure 3, versus time for each experiment. Scale bar 10 mm.

Figure 4. Dose response curve (two experiments) for forskolin-induced redistribution of the PKAc-F64L-S65T-GFP fusion.

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Figure 5. Time from initiation of a response to half maximal ( $t_{1/2\text{max}}$ ) and maximal ( $t_{max}$ ) PKAc-F64L-S65T-GFP redistribution. The data was extracted from curves such as that shown in "Figure 2." All  $t_{1/2\text{max}}$  and  $t_{max}$  values are given as mean±SD and are based on a total of 26-30 cells from 2-3 independent experiments for each forskolin concentration. Since the observed redistribution is sustained over time, the  $t_{max}$  values were taken as the earliest time point at which complete redistribution is reached. Note that the values do not relate to the degree of redistribution.

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Figure 6. Parallel dose response analyses of forskolin induced cAMP elevation and PKAc-F64L-S65T-GFP redistribution. The effects of buffer or 5 increasing concentrations of forskolin on the localisation of the PKAc-F64L-S65T-GFP fusion protein in CHO/PKAc-F64L-S65T-GFP cells, grown in a 96 well plate, were analysed as described above. Computing the ratio of the SD's of fluorescence micrographs taken of the same field of cells, prior to and 30 min after the addition of forskolin, gave a reproducible measure of PKAc-F64L-S65T-GFP redistribution. The graph shows the individual 48 measurements and a trace of their mean±s.e.m at each forskolin concentration. For comparison, the effects of buffer or 8 increasing concentrations of forskolin on [cAMP]<sub>i</sub> was analysed by a scintillation proximity assay of cells grown under the same conditions. The graph shows a trace of the mean ± s.e.m of 4 experiments expressed in arbitrary units.

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Figure 7. BHK cells stably transfected with the human muscarinic (hM1) receptor and the PKCa-F64L-S65T-GFP fusion. Carbachol (100 mM added at 1.0 second) induced a transient redistribution of PKCa-F64L-S65T-GFP from the cytoplasm to the plasma membrane. Images were taken at the following times: a) 1 second before carbachol addition, b) 8.8 seconds after addition and c) 52.8 seconds after addition.

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Figure 8. BHK cells stably transfected with the hM1 receptor and PKCa-F64L-S65T-GFP fusion were treated with carbachol (1 mM, 10 mM, 100 mM). In single cells intracellular [Ca²+] was monitored simultaneously with the redistribution of PKCa-F64L-S65T-GFP. Dashed line indicates the addition times of carbachol. The top panel shows changes in the intracellular Ca²+ concentration of individual cells with time for each treatment. The middle panel shows changes in the average cytoplasmic GFP fluorescence for individual cells against time for each treatment. The bottom panel shows changes in the fluorescence of the periphery of single cells, within regions that specifically include the circumferential edge of a cell as seen in normal projection, the regions which offers best chance to monitor changes in the fluorescence intensity of the plasma membrane.

Figure 9. a) The hERK1-F64L-S65T-GFP fusion expressed in HEK293 cells treated with 100 mM of the MEK1 inhibitor PD98059 in HAM F-12 (without serum) for 30 minutes at 37 °C. The nuclei empty of fluorescence during this treatment.

- b) The same cells as in (a) following treatment with 10 % foetal calf serum for 15 minutes at 37 °C.
- c) Time profiles for the redistribution of GFP fluorescence in HEK293 cells following treatment with various concentrations of EGF in Hepes buffer (HAM F-12 replaced with Hepes buffer directly before the experiment). Redistribution of fluorescence is expressed as the change in the ratio value between areas in nucleus and cytoplasm of single cells. Each time profile is the mean for the changes seen in six single cells.
- d) Bar chart for the end-point measurements, 600 seconds after start of EGF treatments, of fluorescence change (nucleus:cytoplasm) following various concentrations of EGF.

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#### Figure 10.

- a) The SMAD2-EGFP fusion expressed in HEK293 cells starved of serum overnight in HAM F-12. HAM F-12 was then replaced with Hepes buffer pH 7.2 immediately before the experiment. Scale bar is 10 mm.
- b) HEK 293 cells expressing the SMAD2-EGFP fusion were treated with various concentration of TGF-beta as indicated, and the redistribution of fluorescence monitored against time.

The time profile plots represent increases in fluorescence within the nucleus, normalised to starting values in each cell measured. Each trace is the time profile for a single cell nucleus.

c) A bar chart representing the end-point change in fluorescence within nuclei (after 850 seconds of treatment) for different concentrations of TGF-beta. Each bar is the value for a single nucleus in each treatment.

Figure 11. The VASP-F64L-S65T-GFP fusion in CHO cells stably transfected with the human insulin receptor. The cells were starved for two hours in HAM F-12 without serum, then treated with 10% foetal calf serum. The image shows the resulting redistribution of fluorescence after 15 minutes of treatment. GFP fluorescence becomes localised in structures identified as focal adhesions along the length of actin stress fibres.

Figure 12. Time lapse recording GLUT4-GFP redistribution in CHO-HIR cells. Time indicates minutes after the addition of 100 nM insulin.

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### **EXAMPLE 1**

5 Construction, testing and implementation of an assay for cAMP based on PKA activation in real time within living cells.

Useful for monitoring the activity of signalling pathways which lead to altered concentrations of cAMP, e.g. activation of G-protein coupled receptors which couple to G-proteins of the G<sub>s</sub> or G<sub>t</sub> class.

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The catalytic subunit of the murine cAMP dependent protein kinase (PKAc)was fused C-terminally to a F64L-S65T derivative of GFP. The resulting fusion (PKAc-F64L-S65T-GFP) was used for monitoring *in vivo* the translocation and thereby the activation of PKA.

Construction of the PKAc-F64L-S65T-GFP fusion:

15 Convenient restriction endonuclease sites were introduced into the cDNAs encoding murine PKAc (Gen Bank Accession number: M12303) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions were performed according to standard protocols with the following primers:

5'PKAc: TTggACACAAgCTTTggACACCCTCAggATATgggCAACgCCgCCgCCGCCAAg (SEQ ID NO:3),

3'PKAc: gTCATCTTCTCgAgTCTTTCAggCgCgCCCAAACTCAgTAAACTCCTTgCCACAC (SEQ ID NO:4),

5'GFP: TTggACACAAgCTTTggACACggCgCCCATgAgTAAAggAgAACTTTTC (SEQ ID NO:1),

25 3'GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2).

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The PKAc amplification product was then digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. The two digested PCR products were subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion construct (SEQ ID NO:68 & 69) was under control of the SV40 promoter.

Transfection and cell culture conditions.

Chinese hamster ovary cells (CHO), were transfected with the plasmid containing the PKAc-F64L-S65T-GFP fusion using the calcium phosphate precipitate method in HEPES-buffered saline (Sambrook *et al.*, 1989). Stable transfectants were selected using 1000 mg Zeocin/ml (Invitrogen) in the growth medium (DMEM with 1000 mg glucose/l, 10 % fetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml<sup>-1</sup>, 2 mM L-glutamine purchased from Life Technologies Inc., Gaithersburg, MD, USA). Untransfected CHO cells were used as the control. To assess the effect of glucagon on fusion protein translocation, the PKAc-F64L-S65T-GFP fusion was stably expressed in baby hamster kidney cells overexpressing the human glucagon receptor (BHK/GR cells) Untransfected BHK/GR cells were used as the control. Expression of GR was maintained with 500 mg G418/ml (*Neo* marker) andPKAc-F64L-S65T-GFP was maintained with 500 mg Zeocin/ml (*Sh ble* marker). CHO cells were also simultaneously co-transfected with vectors containing the PKAc-F64L-S65T-GFP fusion and the human a2a adrenoceptor (hARa2a).

For fluorescence microscopy, cells were allowed to adhere to Lab-Tek chambered coverglasses (Nalge Nunc Int., Naperville, IL, USA) for at least 24 hours and cultured to about 80% confluence. Prior to experiments, the cells were cultured over night without selection pressure in HAM F-12 medium with glutamax (Life Technologies), 100 mg penicillinstreptomycin mixture ml<sup>-1</sup> and 0.3 % FBS. This medium has low autofluorescence enabling fluorescence microscopy of cells straight from the incubator.

Monitoring activity of PKA activity in real time:

Image aquisition of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a Fluar 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W HBO arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror

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and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

Images were processed and analyzed in the following manner:.

Method 1: Stepwise procedure for quantitation of translocation of PKA:

- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
  - 2. The image was corrected for non-uniformity of the illumination by performing a pixel-bypixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
  - 3. The image histogram, i.e., the frequency of occurrence of each intensity value in the image, was calculated.
  - 4. A smoothed, second derivative of the histogram was calculated and the second zero is determined. This zero corresponds to the inflection point of the histogram on the high side of the main peak representing the bulk of the image pixel values.
  - 5. The value determined in step 4 was subtracted from the image. All negative values were discarded.
  - 6. The variance (square of the standard deviation) of the remaining pixel values was determined. This value represents the "response" for that image.
- 7. Scintillation proximity assay (SPA) for independent quantitation of cAMP:

## Method 2: Alternative method for quantitation of PKA redistribution:

- 1. The fluorescent aggregates are segmented from each image using an automatically found threshold based on the maximisation of the information measure between the object and background. The *a priori* entropy of the image histogram is used as the information measure.
  - 2. The area of each image occupied by the aggregates is calculated by counting pixels in the segmented areas.
- 3. The value obtained in step 2 for each image in a series, or treatment pair, is normalised to the value found for the first (unstimulated) image collected. A value of zero (0) indicates no redistribution of fluorescence from the starting condition. A value of one (1) by this method equals full redistribution.
- 15 Cells were cultured in HAM F-12 medium as described above, but in 96-well plates. The medium was exchanged with Ca<sup>2+</sup>-HEPES buffer including 100 mM IBMX and the cells were stimulated with different concentrations of forskolin for 10 min. Reactions were stopped with addition of NaOH to 0.14 M and the amount of cAMP produced was measured with the cAMP-SPA kit, RPA538 (Amersham) as described by the manufacturer.

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Manipulating intracellular levels of cAMP to test the PKAc-F64L-S65T-GFP fusion.

The following compounds were used to vary cAMP levels: Forskolin, an activator of adenylate cyclase; dbcAMP, a membrane permeable cAMP analog which is not degraded by phosphodiesterase; IBMX, an inhibitor of phosphodiesterase.

- 25 CHO cells stably expressing the PKAc-F64L-S65T-GFP, showed a dramatic translocation of the fusion protein from a punctate distribution to an even distribution throughout the cytoplasm following stimulation with 1 mM forskolin (n=3), 10 mM forskolin (n=4) and 50 mM forskolin (n=4) (Fig 1), or dbcAMP at 1mM (n=6).
  - Fig. 2 shows the progression of response in time following treatment with 1 mM forskolin.

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Fig. 3 gives a comparison of the average temporal profiles of fusion protein redistribution and a measure of the extent of each response to the three forskolin concentrations (Fig. 3A, E, B), and to 1 mM dbcAMP (fig 3C) which caused a similar but slower response, and to addition of 100 mM IBMX (n=4, Fig. 3D) which also caused a slow response, even in the absence of adenylate cyclase stimulation. Addition of buffer (n=2) had no effect (data not shown).

As a control for the behavior of the fusion protein, F64L-S65T-GFP alone was expressed in CHO cells and these were also given 50 mM forskolin (n=5); the uniform diffuse distribution characteristic of GFP in these cells was unaffected by such treatment (data not shown).

The forskolin induced translocation of PKAc-F64L-S65T-GFP showed a dose-response relationship (Fig 4 and 6), see quantitative procedures above.

Reversibility of PKAc-F64L-S65T-GFP translocation.

The release of the PKAc probe from its cytoplasmic anchoring hotspots was reversible. Washing the cells repeatedly (5-8 times) with buffer after 10µM forskolin treatment completely restored the punctate pattern within 2-5 min (n=2, Fig. 3E). In fact the fusion protein returned to a pattern of fluorescent cytoplasmic aggregates virtually indistinguishable from that observed before forskolin stimulation.

To test whether the return of fusion protein to the cytoplasmic aggregates reflected a decreased [cAMP], cells were treated with a combination of 10 mM forskolin and 100 mM IBMX (n=2) then washed repeatedly (5-8 times) with buffer containing 100 mM IBMX (Fig. 3F). In these experiments, the fusion protein did not return to its prestimulatory localization after removal of forskolin.

25 Testing the PKA-F64L-S65T-GFP probe with physiologically relevant agents.

To test the probe's response to receptor activation of adenylate cyclase, BHK cells stably transfected with the glucagon receptor and the PKA-F64L-S65T-GFP probe were exposed to glucagon stimulation. The glucagon receptor is coupled to a G<sub>s</sub> protein which activates adenylate cyclase, thereby increasing the cAMP level. In these cells, addition of 100 nM glucagon (n=2) caused the release of the PKA-F64L-S65T-GFP probe from the cytoplasmic aggregates and a resulting translocation of the fusion protein to a more even cytoplasmic

distribution within 2-3 min (Fig. 3G). Similar but less pronounced effects were seen at lower glucagon concentrations (n=2, data not shown). Addition of buffer (n=2) had no effect over time (data not shown).

Transiently transfected CHO cells expressing hARa2a and the PKA-F64L-S65T-GFP probe were treated with 10 mM forskolin for 7.5 minutes, then, in the continued presence of forskolin, exposed to 10 mM norepinephrine to stimulate the exogenous adrenoreceptors, which couple to a G<sub>I</sub> protein, which inhibit adenylate cyclase. This treatment led to reappearance of fluorescence in the cytoplasmic aggregates indicative of a decrease in [cAMP]<sub>i</sub> (Fig. 3H).

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Fusion protein translocation correlated with [cAMP]i

As described above, the time it took for a response to come to completion was dependent on the forskolin dose (Fig. 5) In addition the degree of responses was also dose dependent. To test the PKA-F64L-S65T-GFP fusion protein translocation in a semi high through-put system, CHO cells stably transfected with the PKA-F64L-S65T-GFP fusion was stimulated with buffer and 5 increasing doses of forskolin (n=8). Using the image analysis algorithm described above (Method 1), a dose response relationship was observed in the range from 0.01-50 mM forskolin (Fig. 6). A half maximal stimulation was observed at about 2 mM forskolin. In parallel, cells were stimulated with buffer and 8 increasing concentrations of forskolin (n=4) in the range 0.01-50 mM. The amount of cAMP produced was measured in an SPA assay. A steep increase was observed between 1 and 5 mM forskolin coincident with the steepest part of the curve for fusion protein translocation (also Fig. 6)

### 25 EXAMPLE 2

Quantitation of redistribution in real-time within living cells.

Probe for detection of PKC activity in real time within living cells:

Construction of PKC-GFP fusion:

The probe was constructed by ligating two restriction enzyme treated polymerase chain reaction (PCR) amplification products of the cDNA for murine PKCα (GenBank Accession number: M25811) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) respectively. Taq® polymerase and the following oligonucleotide primers were used for PCR;

5 5'mPKCa: TTggACACAAgCTTTggACACCCTCAggATATggCTgACgTTTACCCggCCAACg (SEQ ID NO:5),

3'mPKCa: gTCATCTTCTCgAgTCTTTCAggCgCgCCCTACTgCACTTTgCAAgATTgggTgC (SEQ ID NO:6),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTT-TTC (SEQ ID NO:1),

3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2).

The hybrid DNA strand was inserted into the pZeoSV® mammalian expression vector as a HindIII-XhoI casette as described in example 1.

#### 15 Cell Culture:

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BHK cells expressing the human M1 receptor under the control of the inducible metallothionine promoter and maintained with the dihydrofolate reductase marker were transfected with the PKC $\alpha$ -F64L-S65T-GFP probe using the calcium phosphate precipitate method in HEPES buffered saline (HBS [pH 7.10]). Stable transfectants were selected using 1000  $\mu$ g Zeocin®/ml in the growth medium (DMEM with 1000 mg glucose/l, 10 % foetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml-1, 2 mM l-glutamine). The hM1 receptor and PKC $\alpha$ -F64L-S65T-GFP fusion protein were maintained with 500 nM methotrexate and 500  $\mu$ g Zeocin®/ml respectively. 24 hours prior to any experiment, the cells were transferred to HAM F-12 medium with glutamax, 100  $\mu$ g penicillin-streptomycin mixture ml-1 and 0.3 % FBS. This medium relieves selection pressure, gives a low induction of signal transduction pathways and has a low autofluorescence at the relevant wavelength enabling fluorescence microscopy of cells straight from the incubator.

Monitoring the PKC activity in real time:

Digital images of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics

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CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

5 Images were analyzed using the IPLab software package for Macintosh.

Upon stimulation of the M1-BHK cells, stably expressing the PKC $\alpha$ -F64L-S65T-GFP fusion, with carbachol we observed a dose-dependent transient translocation from the cytoplasm to the plasma membrane (Fig. 7a,b,c). Simultaneous measurement of the cytosolic free calcium concentration shows that the carbachol-induced calcium mobilisation precedes the translocation (Fig. 8).

Stepwise procedure for quantitation of translocation of PKC:

- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
- 2. The image was corrected for non-uniformity of the illumination by performing a pixel-bypixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
  - 3. A copy of the image was made in which the edges are identified. The edges in the image are found by a standard edge-detection procedure convolving the image with a kernel which removes any large-scale unchanging components (i.e., background) and accentuates any small-scale changes (i.e., sharp edges). This image was then converted to a binary image by threshholding. Objects in the binary image which are too small to represent the edges of cells were discarded. A dilation of the binary image was performed to close any gaps in the image edges. Any edge objects in the image which were in contact with the borders of the image are discarded. This binary image represents the edge mask.
  - 4. Another copy of image was made via the procedure in step 3. This copy was further processed to detect objects which enclose "holes" and setting all pixels inside the holes to the binary value of the edge, i.e., one. This image represents the whole cell mask.
- 5. The original image was masked with the edge mask from step 3 and the sum total of all pixel values is determined.

- 6. The original image was masked with the whole cell mask from step 4 and the sum total of all pixel values was determined.
- 7. The value from step 5 was divided by the value from step 6 to give the final result, the fraction of fluorescence intensity in the cells which was localized in the edges.

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### **EXAMPLE 3**

Probes for detection of mitogen activated protein kinase Erk1 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk1, a serine/threonine protein kinase, is a component of a signalling pathway which is activated by e.g. many growth factors.

Probes for detection of ERK-1 activity in real time within living cells:

- The extracellular signal regulated kinase (ERK-1, a mitogen activated protein kinase, MAPK) is fused N- or C-terminally to a derivative of GFP. The resulting fusions expressed in different mammalian cells are used for monitoring *in vivo* the nuclear translocation, and thereby the activation, of ERK1 in response to stimuli that activate the MAPK pathway.
  - a) Construction of murine ERK1 F64L-S65T-GFP fusion:
- 20 Convenient restriction endonuclease sites are introduced into the cDNAs encoding murine ERK1 (GenBank Accession number: Z14249) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions are performed according to standard protocols with the following primers:
- 5'ERK1: TTggACACAAgCTTTggACACCCTCAggATATggCggCggCggCggCggCggCTCCggggggCgggg (SEQ ID NO:7),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTT-TTC (SEQ ID NO:1)

5 3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2)

To generate the mERK1-F64L-S65T-GFP (SEQ ID NO:56 & 57) fusion the ERK1 amplification product is digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. To generate the F64L-S65T-GFP-mERK1 fusion the ERK1 amplification product is then digested with HindIII+Bsu36I and the F64L-S65T-GFP product with Bsu36I+XhoI. The two pairs of digested PCR products are subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion constructs are under control of the SV40 promoter.

b) The human Erk1 gene (GenBank Accession number: X60188) was amplified using PCR according to standard protocols with primers Erk1-top (SEQ ID NO:9) and Erk1-bottom/+stop (SEQ ID NO:10). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Erk1 fusion
 (SEQ ID NO:38 &39) under the control of a CMV promoter.

The plasmid containing the EGFP-Erk1 fusion was transfected into HEK293 cells employing the FUGENE transfection reagent (Boehringer Mannheim). Prior to experiments the cells were grown to 80%-90% confluency 8 well chambers in DMEM with 10% FCS. The cells were washed in plain HAM F-12 medium (without FCS), and then incubated for 30-60 minutes in plain HAM F-12 (without FCS) with 100 micromolar PD98059, an inhibitor of MEK1, a kinase which activates Erk1; this step effectively empties the nucleus of EGFP-Erk1. Just before starting the experiment, the HAM F-12 was replaced with Hepes buffer following a wash with Hepes buffer. This removes the PD98059 inhibitor; if blocking of MEK1 is still wanted (e.g. in control experiments), the inhibitor is included in the Hepes buffer.

The experimental setup of the microscope was as described in example 1.

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60 images were collected with 10 seconds between each, and with the test compound added after image number 10.

Addition of EGF (1-100 nM) caused within minutes a redistribution of EGFP-Erk1 from the cytoplasm into the nucleus (Fig. 9a,b).

The response was quantitated as described below and a dose-dependent relationship between EGF concentration and nuclear translocation of EGFP-Erk1 was found (Fig. 9c,d). Reditribution of GFP fluorescence is expressed in this example as the change in the ratio value between areas in nuclear versus cytoplasmic compartments of the cell. Each time profile is the average of nuclear to cytoplasmic ratios from six cells in each treatment.

### **EXAMPLE 4:**

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Probes for detection of Erk2 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk2, a serine/threonine protein kinase, is closely related to Erk1 but not identical; it is a component of a signalling pathway which is activated by e.g. many growth factors.

- a) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers Erk2-top (SEQ ID NO:11) and Erk2-bottom/+stop (SEQ ID NO:13) The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-Erk2 fusion (SEQ ID NO:40 &41) under the control of a CMV promoter.
- b) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers (SEQ ID NO:11) Erk2-top and Erk2-bottom/-stop (SEQ ID NO:12). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an Erk2-EGFP fusion (SEQ ID NO:58 &59) under the control of a CMV promoter.

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The resulting plasmids were transfected into CHO cells and BHK cells. The cells were grown under standard conditions. Prior to experiments, the cells were starved in medium without serum for 48-72 hours. This led to a predominantly cytoplasmic localization of both probes, especially in BHK cells. 10% fetal calf serum was added to the cells and the fluorescence of the cells was recorded as explained in example 3. Addition of serum caused the probes to redistribute into the nucleus within minutes of addition of serum.

#### **EXAMPLE 5:**

10 Probes for detection of Smad2 redistribution.

Useful for monitoring signalling pathways activated by some members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad 2, a signal transducer, is a component of a signalling pathway which is induced by some members of the TGFbeta family of cytokines.

- a) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/+stop (SEQ ID NO:26). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with EcoR1 and Acc65I. This produces an EGFP-Smad2 fusion (SEQ ID NO:50&51) under the control of a CMV promoter.
- b) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/-stop (SEQ ID NO:25). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces a Smad2-EGFP fusion (SEQ ID NO:74 &75) under the control of a CMV promoter.
- The plasmid containing the EGFP-Smad2 fusion was transfected into HEK293 cells, where it showed a cytoplasmic distribution. Prior to experiments the cells were grown in 8 well Nunc

chambers in DMEM with 10% FCS to 80% confluency and starved overnight in HAM F-12 medium without FCS.

For experiments, the HAM F-12 medium was replaced with Hepes buffer pH 7.2.

The experimental setup of the microscope was as described in example 1.

5 90 images were collected with 10 seconds between each, and with the test compound added after image number 5.

After serum starvation of cells, each nucleus contains less GFP fluorescence than the surrounding cytoplasm (Fig. 10a). Addition of TGFbeta caused within minutes a redistribution of EGFP-Smad2 from the cytoplasma into the nucleus (Fig. 10b).

The redistribution of fluorescence within the treated cells was quantified simply as the fractional increase in nuclear fluorescence normalised to the starting value of GFP fluorescence in the nucleus of each unstimulated cell.

### 15 EXAMPLE 6:

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Probe for detection of VASP redistribution.

Useful for monitoring signalling pathways involving rearrangement of cytoskeletal elements, e.g. to identify compounds which modulate the activity of the pathway in living cells.

VASP, a phosphoprotein, is a component of cytoskeletal structures, which redistributes in response to signals which affect focal adhesions.

a) The human VASP gene (GenBank Accession number: Z46389) was amplified using PCR according to standard protocols with primers VASP-top (SEQ ID NO:94) and VASP-bottom/+stop (SEQ ID NO:95). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produces an EGFP-VASP fusion (SEQ ID NO:124 &125) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor using the calcium-phosphate transfection method. Prior to experiments, cells were grown in 8 well Nunc chambers and starved overnight in medium without FCS.

Experiments are performed in a microscope setup as described in example 1.

10% FCS was added to the cells and images were collected. The EGFP-VASP fusion was redistributed from a somewhat even distribution near the periphery into more localized structures, identified as focal adhesion points (Fig. 11).

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A large number of further GFP fusions have been made or are in the process of being made, as apparent from the following Examples 7-22 which also suggest suitable host cells and substances for activation of the cellular signalling pathways to be monitored and analyzed.

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## **EXAMPLE 7**:

Probe for detection of actin redistribution.

Useful for monitoring signalling pathways involving rearrangement or formation of actin filaments, e.g. to identify compounds which modulate the activity of pathways leading to cytoskeletal rearrangements in living cells.

Actin is a component of cytoskeletal structures, which redistributes in response to very many cellular signals.

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The actin binding domain of the human alpha-actinin gene (GenBank Accession number: X15804) was amplified using PCR according to standard protocols with primers ABD-top (SEQ ID NO:90) and ABD-bottom/-stop (SEQ ID NO:91). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and BamH1. This produced an actin-binding-domain-EGFP fusion (SEQ ID NO:128 &129) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor. Cells were stimulated with insulin which caused the actin binding domain-EGFP probe to become redistributed into morphologically distinct membrane-associated structures.

# Example 8:

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Probes for detection of p38 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

p38, a serine/thronine protein kinase, is a component of a stress-induced signalling pathway which is activated by many types of cellular stress, e.g. TNFalpha, anisomycin, UV and mitomycin C.

- a) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:14) and p38-bottom/+stop (SEQ ID NO: 16). The PCR product was digested with restriction enzymes
   Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-p38 fusion (SEQ ID NO:46 &47) under the control of a CMV promoter.
  - b) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:13) and p38-bottom/-stop (SEQ ID NO:15). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a p38-EGFP fusion (SEQ ID NO:64 &65) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-p38 probe and/or the p38-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear within minutes in response to activation of the signal-ling pathway with e.g. anisomycin.

### Example 9:

30 Probes for detection of Jnk1 redistribution.

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Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

Jnk1, a serine/threonine protein kinase, is a component of a stress-induced signalling pathway different from the p38 described above, though it also is activated by many types of cellular stress, e.g. TNFalpha, anisomycin and UV.

- a) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/+stop (SEQ ID NO:19). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-Jnk1 fusion (SEQ ID NO:44 &45) under the control of a CMV promoter.
- b) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/-stop (SEQ ID NO:18). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a Jnk1-EGFP fusion (SEQ ID NO:62 &63) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-Jnk1 probe and/or the Jnk1-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. anisomycin.

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### Example 10:

Probes for detection of PKG redistribution.

Useful for monitoring signalling pathways involving changes in cyclic GMP levels, e.g. to identify compounds which modulate the activity of the pathway in living cells.

30 PGK, a cGMP-dependent serine/threonine protein kinase, mediates the guanylyl-cyclase/cGMP signal.

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- a) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/+stop (SEQ ID NO:83). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKG fusion (SEQ ID NO:134 &135) under the control of a CMV promoter.
- b) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/-stop
   (SEQ ID NO: 82) . The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a PKG-EGFP fusion (SEQ ID NO:136 &137) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. A10, in which the EGFP-PKG probe and/or the PKG-EGFP probe should change its cellular distribution from cyto-plasmic to one associated with cytoskeletal elements within minutes in response to treatment with agents which raise nitric oxide (NO) levels.

## Example 11:

- 20 Probes for detection of IkappaB kinase redistribution.
  - Useful for monitoring signalling pathways leading to NFkappaB activation, e.g. to identify compounds which modulate the activity of the pathway in living cells.
  - IkappaB kinase, a serine/threonine kinase, is a component of a signalling pathway which is activated by a variety of inducers including cytokines, lymphokines, growth factors and stress.
  - a) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/+stop (SEQ ID NO:98). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-C1 (Clontech, Palo Alto;

GenBank Accession number U55763) digested with EcoR1and Acc65I. This produces an EGFP-IkappaB-kinase fusion (SEQ ID NO:120 &121) under the control of a CMV promoter.

b) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/-stop (SEQ ID NO:97). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces an IkappaB-kinase-EGFP fusion (SEQ ID NO:122 &123) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the

EGFP-lkappaB-kinase probe and/or the lkappaB-kinase-EGFP probe should achieve a more
cytoplasmic distribution within seconds following stimulation with e.g. TNFalpha.

### Example 12:

Probes for detection of CDK2 redistribution.

Useful for monitoring signalling pathways of the cell cycle, e.g. to identify compounds which modulate the activity of the pathway in living cells.

CDK2, a cyclin-dependent serine/threonine kinase, is a component of the signalling system which regulates the cell cycle.

- a) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/+stop (SEQ ID NO: 104). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-CDK2 fusion (SEQ ID NO:114 &115) under the control of a CMV promoter.
  - b) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/-stop (SEQ ID NO:103). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a CDK2-EGFP fusion (SEQ ID NO:112 &113) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 in which the EGFP-CDK2 probe and/or the CDK2-EGFP probe should change its cellular distribution from cytoplasmic in contact-inhibited cells, to nuclear location in response to activation with a number of growth factors, e.g. IGF.

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### Example 13:

Probes for detection of Grk5 redistribution.

Useful for monitoring signalling pathways involving desensitization of G-protein coupled receptors, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Grk5, a G-protein coupled receptor kinase, is a component of signalling pathways involving membrane bound G-protein coupled receptors.

- a) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-
- bottom/+stop (SEQ ID NO:29). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Grk5 fusion (SEQ ID NO:42 &43) under the control of a CMV promoter.
  - b) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/-stop (SEQ ID NO:28). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Grk5-EGFP fusion (SEQ ID NO:60 &61) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 expressing a rat dopamine D1A receptor, in which the EGFP-Grk5 probe and/or the Grk5-EGFP probe should change its cellular distribution from predominantly cytoplasmic to peripheral in response to activation of the signalling pathway with e.g. dopamine.

30 Example 14:

WO 98/45704 PCT/DK98/00145

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Probes for detection of Zap70 redistribution.

Useful for monitoring signalling pathways involving the T cell receptor, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Zap70, a tyrosine kinase, is a component of a signalling pathway which is active in e.g. T-cell differentiation.

- a) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/+stop (SEQ ID NO:107). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Zap70 fusion (SEQ ID NO:108 &109) under the control of a CMV promoter.
- b) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70 bottom/-stop (SEQ ID NO:106). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Zap70-EGFP fusion (SEQ ID NO:110 &111) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-Zap70 probe and/or the Zap70-EGFP probe should change its cellular distribution from cytoplasmic to membrane-associated within seconds in response to activation of the T cell receptor signalling pathway with e.g. antibodies to CD3epsilon.

## Example 15:

25 Probes for detection of p85 redistribution.

Useful for monitoring signalling pathways involving PI-3 kinase, e.g. to identify compounds which modulate the activity of the pathway in living cells.

p85alpha is the regulatory subunit of PI3-kinase which is a component of many pathways involving membrane-bound tyrosine kinase receptors and G-protein-coupled receptors.

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- a) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-C (SEQ ID NO:22) and p85-bottom/+stop (SEQ ID NO:23). The PCR product was digested with restriction enzymes Bgl2 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Bgl2 and BamH1. This produced an EGFP-p85alpha fusion (SEQ ID NO:48 &49) under the control of a CMV promoter.
- b) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-N (SEQ ID NO:20) and p85-bottom/-stop (SEQ ID NO:21). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a p85alpha-EGFP fusion (SEQ ID NO:66 &67) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-p85 probe and/or the p85-EGFP probe may change its cellular distribution from cytoplasmic to membrane-associated within minutes in response to activation of the receptor with insulin.

# Example 16:

Probes for detection of protein-tyrosine phosphatase redistribution.

- Useful for monitoring signalling pathways involving tyrosine kinases, e.g. to identify compounds which modulate the activity of the pathway in living cells.
  - Protein-tyrosine phosphatase1C, a tyrosine-specific phosphatase, is an inhibitory component in signalling pathways involving e.g. some growth factors.
- a) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/+stop (SEQ ID NO:101). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-PTP fusion (SEQ ID NO:116 &117) under the control of a CMV promoter.

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b) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/-stop (SEQ ID NO:100). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces a PTP-EGFP fusion (SEQ ID NO:118 &119) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MCF-7 in which the EGFP-PTP probe and/or the PTP-EGFP probe should change its cellular distribution from cytoplasm to the plasma menbrane within minutes in response to activation of the growth inhibitory signalling pathway with e.g. somatostatin.

## Example 17:

Probes for detection of Smad4 redistribution.

Useful for monitoring signalling pathways involving most members of the transforming

growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad4, a signal transducer, is a common component of signalling pathways induced by various members of the TGFbeta family of cytokines.

- a) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top and Smad4-bottom/+stop (SEQ ID NO:35). The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produce an EGFP-Smad4 fusion (SEQ ID NO:52 &53) under the control of a CMV promoter.
  - b) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top (SEQ ID NO:33) and Smad4-bottom/-stop (SEQ ID NO:34). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a Smad4-EGFP fusion (SEQ ID NO:76 &77) under the control of a CMV promoter.

The resulting plasmids are transfected into a cell line, e.g. HEK293 in which the EGFP-Smad4 probe and/or the Smad4-EGFP probe should change its cellular distribution within minutes from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TGFbeta.

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## Example 18:

Probes for detection of Stat5 redistribution.

Useful for monitoring signalling pathways involving the activation of tyrosine kinases of the Jak family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Stat5, signal transducer and activator of transcription, is a component of signalling pathways which are induced by e.g. many cytokines and growth factors.

- a) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/+stop (SEQ ID NO:32). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with Bgl2 and Acc65I. This produced an EGFP-Stat5 fusion (SEQ ID NO:54 &55) under the control of a CMV promoter.
- b) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/stop (SEQ ID NO:331). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Bgl2 and Acc65I. This produced a Stat5-EGFP fusion (SEQ ID NO:78
   &79) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MIN6 in which the EGFP-Stat5 probe and/or the Stat5-EGFP probe should change its cellular distribution from cyto-plasmic to nuclear within minutes in response to activation signalling pathway with e.g. prolactin.

Example 19:

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Probes for detection of NFAT redistribution.

Useful for monitoring signalling pathways involving activation of NFAT, e.g. to identify compounds which modulate the activity of the pathway in living cells.

5 NFAT, an activator of transcription, is a component of signalling pathways which is involved in e.g. immune responses.

- a) The human NFAT1 gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/+stop (SEQ ID NO:86). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-NFAT fusion (SEQ ID NO:130 &131) under the control of a CMV promoter.
- b) The human NFAT gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/stop (SEQ ID NO:85). The PCR product is digested with restriction enzymes Xho1 and E-coR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces an NFAT-EGFP fusion (SEQ ID NO:132 &133) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFAT probe and/or the NFAT-EGFP probe should change its cellular distribution from cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. antibodies to CD3epsilon.

## 25 Example 20:

Probes for detection of NFkappaB redistribution.

Useful for monitoring signalling pathways leading to activation of NFkappaB, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFkappaB, an activator of transcription, is a component of signalling pathways which are responsive to a varity of inducers including cytokines, lymphokines, some immunosuppressive agents.

- a) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/+stop (SEQ ID NO:89). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-NFkappaB fusion (SEQ ID NO:142 & 143) under the control of a CMV promoter.
  - b) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/-stop (SEQ ID NO:88). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an NFkappaB-EGFP fusion (SEQ ID NO:140 & 141) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFkappaB probe and/or the NFkappaB-EGFP probe should change its cellular distribution from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TNFalpha.

### Example 21:

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Probe for detection of RhoA redistribution.

Useful for monitoring signalling pathways involving RhoA, e.g. to identify compounds which modulate the activity of the pathway in living cells.

RhoA, a small GTPase, is a component of many signalling pathways, e.g. LPA induced cytoskeletal rearrangements.

The human RhoA gene (GenBank Accession number: L25080) was amplified using PCR according to standard protocols with primers RhoA-top (SEQ ID NO:92) and RhoA-bottom/+stop (SEQ ID NO:93). The PCR product was digested with restriction enzymes

Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produced an EGFP-RhoA fusion (SEQ ID NO:126 &127) under the control of a CMV promoter.

The resulting plasmid is transfected into a suitable cell line, e.g. Swiss3T3, in which the EGFP-RhoA probe should change its cellular distribution from a reasonably homogenous to a peripheral distribution within minutes of activation of the signalling pathway with e.g. LPA. Example 22:

Probes for detection of PKB redistribution.

Useful for monitoring signalling pathways involving PKB e.g. to identify compounds which modulate the activity of the pathway in living cells.

PKB, a serine/threonine kinase, is a component in various signalling pathways, many of which are activated by growth factors.

- a) The human PKB gene (GenBank Accession number: M63167) is amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/+stop (SEQ ID NO:80). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKB fusion (SEQ ID NO:138 & 139) under the control of a CMV promoter.
- b) The human PKB gene (GenBank Accession number: M63167) was amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/stop (SEQ ID NO:37). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a PKB-EGFP fusion (SEQ ID NO:70 &71) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-PKB probe and/or the PKB-EGFP probe cycles between cytoplasmic and membrane locations during the activation-deactivation process following addition of insulin. The transition should be apparent within minutes.

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WO 98/45704 PCT/DK98/00145

57

# SEQUENCE LISTING

5	(1) GENERAL INFORMATION
	(i) APPLICANT: NovoNordisk, BioImage
10	(ii) TITLE OF THE INVENTION: A Method of Detecting Cellular Translocation of Biologically Active Polypeptides Using Fluorescense Imaging
	(iii) NUMBER OF SEQUENCES: 143
15	<ul><li>(iv) CORRESPONDENCE ADDRESS:</li><li>(A) ADDRESSEE: NovoNordisk, BioImage</li><li>(B) STREET: Mørkhøjbygade 28</li><li>(C) CITY: Søborg</li></ul>
20	(D) STATE: DK (E) COUNTRY: DENMARK (F) ZIP: 2860
25	<ul> <li>(v) COMPUTER READABLE FORM:</li> <li>(A) MEDIUM TYPE: Diskette</li> <li>(B) COMPUTER: IBM Compatible</li> <li>(C) OPERATING SYSTEM: DOS</li> <li>(D) SOFTWARE: FastSEQ for Windows Version 2.0</li> </ul>
	(b) Software. Fastsey for Windows Version 2.0
30	<pre>(viii) ATTORNEY/AGENT INFORMATION:   (A) NAME: , PV&amp;P R   (B) REGISTRATION NUMBER:   (C) REFERENCE/DOCKET NUMBER:</pre>
35	(2) INFORMATION FOR SEQ ID NO:1:
40	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 53 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>
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55	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear

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	(b) 10F0D031. IIIIeal	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:	
	(AI) Digomici bilonizitoni dig ib novili	
	TAGGATCCAT AGATCTGTAT CCTGG	25
25	(2) INFORMATION FOR SEQ ID NO:13:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 26 base pairs	
30	(B) TYPE: nucleic acid	
30	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(2) ISIGMOST TIMEME	
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:	
35	TAGGATCCTT AAGATCTGTA TCCTGG	26
	(a)	
	(2) INFORMATION FOR SEQ ID NO:14:	
40	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 28 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
45	(b) Torologi. Timedi	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:	
	ATCTCGAGGG AAAATGTCTC AGGAGAGG	28
50	(2) INFORMATION FOR SEQ ID NO:15:	
	(i) SEQUENCE CHARACTERISTICS:	
55	(A) LENGTH: 28 base pairs (B) TYPE: nucleic acid	
ວວ	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
	(o) Diamonico Dingle	

(D) TOPOLOGY: linear

5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:	
3	ATGGATCCTC GGACTCCATC TCTTCTTG	28
	(2) INFORMATION FOR SEQ ID NO:16:	
10	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 29 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
15	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:	
20	ATGGATCCTC AGGACTCCAT CTCTTCTTG	29
20	(2) INFORMATION FOR SEQ ID NO:17:	
25	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 28 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:	
	GTCTCGAGCC ATCATGAGCA GAAGCAAG	28
35	(2) INFORMATION FOR SEQ ID NO:18:	
40	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:	
45	GTGGATCCCA CTGCTGCACC TGTGCTA	27
	(2) INFORMATION FOR SEQ ID NO:19:	
50	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
55	(wi) appropriate the control of the	
•	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:	

	GTGGATCCTC ACTGCTGCAC CTGTGCTA	28
_	(2) INFORMATION FOR SEQ ID NO:20:	
5	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 40 base pairs (B) TYPE: nucleic acid	
10	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
10	(b) TOPOLOGI: Tilleal	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:	
15	CGCGAATTCC GCCACCATGA GTGCTGAGGG GTACCAGTAC	40
	(2) INFORMATION FOR SEQ ID NO:21:	
	(i) SEQUENCE CHARACTERISTICS:	
20	(A) LENGTH: 32 base pairs (B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
25		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:	
	CGCGGATCCT GTCGCCTCTG CTGTGCATAT AC	32
30	(2) INFORMATION FOR SEQ ID NO:22:	
	(i) SEQUENCE CHARACTERISTICS:	
	<ul><li>(A) LENGTH: 30 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
35	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(vi) ORIGINAL SOURCE:	
40	(A) ORGANISM: p85-top-C	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:	
	GGGAGATCTA TGAGTGCTGA GGGGTACCAG	30
45	(2) INFORMATION FOR SEQ ID NO:23:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 34 base pairs (B) TYPE: nucleic acid	
50	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:	
55		3.4
	GGGCGGATCC TCATCGCCTC TGCTGTGCAT ATAC	34 62

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	(2) INFORMATION FOR SEQ ID NO:24:	
5	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 33 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:	
	GTGAATTCGA CCATGTCGTC CATCTTGCCA TTC	33
15	(2) INFORMATION FOR SEQ ID NO:25:	
20	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 31 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:	
	GTGGTACCCA TGACATGCTT GAGCAACGCA C	31
	(2) INFORMATION FOR SEQ ID NO:26:	
30	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 32 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
35	(b) TOPOLOGI: Timear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:	
40	GTGGTACCTT ATGACATGCT TGAGCAACGC AC	32
	(2) INFORMATION FOR SEQ ID NO:27:	
45	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:	
	GTGAATTCGT CAATGGAGCT GGAAAACATC G	31
	(2) INFORMATION FOR SEQ ID NO:28:	
55	(i) SEQUENCE CHARACTERISTICS:	
		63

5	<ul><li>(A) LENGTH: 30 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:	
40	GTGGATCCCT GCTGCTTCCG GTGGAGTTCG	30
10	(2) INFORMATION FOR SEQ ID NO:29:	
	(i) SEQUENCE CHARACTERISTICS:	
15	<ul><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:	
	GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	31
25	(2) INFORMATION FOR SEQ ID NO:30:	
25	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid	
30	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:	
35	GTAGATCTAC CATGGCGGGC TGGATCCAGG CC	32
	(2) INFORMATION FOR SEQ ID NO:31:	
40	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
45		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:	
	GTGGTACCCA TGAGAGGGAG CCTCTGGCAG A	31
50	(2) INFORMATION FOR SEQ ID NO:32:	
55	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:	
5	GTGGTACCTC ATGAGAGGGA GCCTCTGGCA G	31
	(2) INFORMATION FOR SEQ ID NO:33:	
10	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 33 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:	
	GTGAATTCAA CCATGGACAA TATGTCTATT ACG	33
20	(2) INFORMATION FOR SEQ ID NO:34:	
25	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 31 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:	
30	GTGGATCCCA GTCTAAAGGT TGTGGGTCTG C	31
	(2) INFORMATION FOR SEQ ID NO:35:	
35	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 32 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
40	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:	
45	GTGGATCCTC AGTCTAAAGG TTGTGGGTCT GC	32
43	(2) INFORMATION FOR SEQ ID NO:36:	
50	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 27 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:	

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	30												
	GTCTCGAGGC ACCATGAGCG ACGTGGC	27											
	(2) INFORMATION FOR SEQ ID NO:37:												
5 10	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>												
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:												
	TGGGATCCGA GGCCGTGCTG CTGGCCG												
15	(2) INFORMATION FOR SEQ ID NO:38:												
20	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 1896 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>												
25	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:												
30	<ul><li>(A) NAME/KEY: Coding Sequence</li><li>(B) LOCATION: 11891</li><li>(D) OTHER INFORMATION:</li><li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:</li></ul>												
35	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu  1 5 10 15	48											
	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30	96											
40	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 40 45	144											
45	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC  Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr  50 55 60	192											
50	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 65 70 75 80	240											
55	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95	288											

						GGC Gly 105							336
5						GTG Val							384
10						ATC Ile							432
15						ATC Ile							480
20						CGC Arg							528
20						CAG Gln 185							576
25						TAC Tyr							624
30						GAT Asp					_	_	672
35						GGC Gly		Glu					720
						TCG Ser							768
40						GAG Glu 265							816
45						GAG Glu				Gln			864
50		Gly			Gln	TTG Leu			Gly				912
55	Gly			Ala		GAC Asp		Arg				GTG Val	960

	GCC Ala														1008
5	ACG Thr													_	1056
10	ATC Ile									CTG Leu					1104
15	GAT Asp									GAC Asp 380					1152
20										TGC Cys					1200
										GCC Ala					1248
25										ACC Thr					1296
30										GAT Asp					1344
35										CGC Arg 460	Trp				1392
40										Lys				ATC Ile 480	1440
.0					Ile				Leu					ATC	1488
45				His				Leu					Gly	ATC Ile	1536
50			Pro				Lev					e Asr		AAG Lys	1584
55		y Asr				: Le					: Lys			TGG Trp	1632

WO 98/45704 PCT/DK98/00145

09																	
											GCC Ala 555						1680
5											ATC Ile						1728
10											GAC Asp						1776
15											GAG Glu						1824
20											GAG Glu						1872
20				CTG Leu				CTAG									1896
25	(2) INFORMATION FOR SEQ ID NO:39:																
30	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 631 amino acids</li> <li>(B) TYPE: amino acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>																
35	<pre>(ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:</pre>																
40	1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val			15	Leu Gly	
	Glu	Gly	Glu 35	20 Gly	Asp	Ala	Thr	Tyr 40	25 Gly	Lys	Leu	Thr	Leu 45	30 Lys	Phe	Ile	
45		50			_		55					60				Thr Lys	
E0	65				Phe	70				Pro	75				G1n	80 Glu	
50				100					105					110	1	Glu	
55			115					120					125			Gly Tyr	
		130		•		-	135				•	140				-	

	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln		Asn 160
	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
5	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
	oro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
10	Ser	Lys 210	qaA	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
			Arg		245					250					255	
15			Gln	260					265					270		
	-		Gly 275					280					285			
20	=	290	Gly		_	-	295				_	300				
	305	_	Met			310					315					320
			Lys	_	325					330			_		335	
25			Arg	340					345	_		_		350		
		_	Ile 355	_	_			360					365			
30	_	370	Tyr				375					380				
	385	_	Ser Leu			390			_		395					400
35			Leu	_	405		_	-		410					415	
			Cys	420					425					430		
	_		435 Gly					440					445			
40		450	_				455	_				460				
	465		Val			470					475					480
45			Gly		485					490					495	
			Ser	500					505					510		
		-	515 Asn					520			_		525			
50		530					535	•				540	)			
	545	_	. Leu			550	I			_	555	<b>;</b>				560
55			His		565					570	<b>;</b>				575	
				580					585	_	•			590		

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Val Ala Glu Glu Pro Phe Thr Phe Ala Met Glu Leu Asp Asp Leu Pro 600 605 Lys Glu Arg Leu Lys Glu Leu Ile Phe Gln Glu Thr Ala Arg Phe Gln 615 Pro Gly Val Leu Glu Ala Pro (2) INFORMATION FOR SEQ ID NO:40: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1818 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 15 (ii) MOLECULE TYPE: cDNA (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1815 20 (D) OTHER INFORMATION: (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40: 25 ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu GTC GAG CTG GAC GGC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96 30 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 40 CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 45 CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336 50 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 55 115 120

		TTC Phe									_		432
5		AAC Asn								_			480
10		AAG Lys									_		528
15		CTC Leu											576
20		CTG Leu 195											624
20		GAC Asp											672
25		GCC Ala											720
30		AGA Arg											768
35		GTC Val											816
40		TAC Tyr 275											864
40		CTC Leu				Val							912
45	His				Gln				, Glu			CTA Leu 320	960
50				Glu				Ile				CGG Arg	1008
55			Glu				Val				ı Asp	C CTC	1056

										73							
	ATG Met	GAG Glu	ACA Thr 355	GAT Asp	CTT Leu	TAC Tyr	AAG Lys	CTC Leu 360	TTG Leu	AAG Lys	ACA Thr	CAG Gln	CAC His 365	CTC Leu	AGC Ser	AAT Asn	1104
5	Asp	His 370	Ile	TGC Cys	Tyr	Phe	Leu 375	Tyr	Gln	Ile	Leu	Arg 380	Gly	Leu	Lys	Tyr	1152
10	ATA Ile 385	CAT His	TCA Ser	GCT Ala	AAT Asn	GTT Val 390	CTG Leu	CAC His	CGT Arg	GAC Asp	CTC Leu 395	AAG Lys	CCT Pro	TCC Ser	AAC Asn	CTC Leu 400	1200
15	CTG Leu	CTG Leu	AAC Asn	ACC Thr	ACT Thr 405	TGT Cys	GAT Asp	CTC Leu	AAG Lys	ATC Ile 410	TGT Cys	GAC Asp	TTT Phe	GGC Gly	CTT Leu 415	GCC Ala	1248
20				GAT Asp 420													1296
				CGT Arg													1344
25	GGT Gly	TAT Tyr 450	ACC Thr	AAG Lys	TCC Ser	ATT Ile	GAT Asp 455	ATT Ile	TGG Trp	TCT Ser	GTG Val	GGC Gly 460	TGC Cys	ATC Ile	CTG Leu	GCA Ala	1392
30	GAG Glu 465	ATG Met	CTA Leu	TCC Ser	AAC Asn	AGG Arg 470	CCT Pro	ATC Ile	TTC Phe	CCA Pro	GGA Gly 475	AAG Lys	CAT His	TAC Tyr	CTT Leu	GAC Asp 480	1440
35	CAG Gln	CTG Leu	AAT Asn	CAC His	ATC Ile 485	CTG Leu	GGT Gly	ATT Ile	CTT Leu	GGA Gly 490	TCT Ser	CCA Pro	TCA Ser	CAG Gln	GAA Glu 495	GAT Asp	1488
40	CTG Leu	AAT Asn	TGT Cys	ATA Ile 500	ATA Ile	AAT Asn	TTA Leu	AAA Lys	GCT Ala 505	AGA Arg	AAC Asn	TAT Tyr	TTG Leu	CTT Leu 510	TCT Ser	CTC Leu	1536
	CCG Pro	CAC His	AAA Lys 515	AAT Asn	AAG Lys	GTG Val	CCG Pro	TGG Trp 520	AAC Asn	AGG Arg	TTG Leu	TTC Phe	CCA Pro 525	AAC Asn	GCT Ala	GAC Asp	1584
45	TCC Ser	AAA Lys 530	GCT Ala	CTG Leu	GAT Asp	TTA Leu	CTG Leu 535	GAT Asp	AAA Lys	ATG Met	TTG Leu	ACA Thr 540	TTT Phe	AAC Asn	CCT Pro	CAC His	1632
50	AAG Lys 545	AGG Arg	ATT Ile	GAA Glu	GTT Val	GAA Glu 550	CAG Gln	GCT Ala	CTG Leu	GCC Ala	CAC His 555	CCG Pro	TAC Tyr	CTG Leu	GAG Glu	CAG Gln 560	1680
55	TAT Tyr	TAT Tyr	GAC Asp	CCA Pro	AGT Ser 565	GAT Asp	GAG Glu	CCC Pro	ATT Ile	GCT Ala 570	GAA Glu	GCA Ala	CCA Pro	TTC Phe	AAG Lys 575	TTT Phe	1728

			GAG Glu														1776
5			GAG Glu 595											TAA			1818
10			(2)	INF	ORMA	MOIT	FOF	SEC	Q ID	NO:4	1:						
15		(i	(B) (C)	QUEN LENG TYPE STRA TOPO	TH: : an NDEI	605 mino ONESS	amir acio 3: si	no ao i ingle	cids								
20		(1	li) M 7) FF ci) S	RAGME	ENT T	CYPE:	int	erna	al	מו נ	NO:4	<b>:</b> 1:					
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
25	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
30	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	FÀS	
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu	
35	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120		Asn	Arg	Ile	Glu 125	Leu	Lys	Gly	
40	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135		Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr	
	Asn 145	Tyr	Asn	Ser	His	Asn 150		Tyr	Ile	Met	Ala 155		Lys	Gln	ГЛЗ	Asn 160	
		Ile	Lys	Val	Asn 165	Phe		Ile	Arg	His 170	Asn		Glu	Asp	Gly 175		
45	Val	Gln	Leu	Ala 180			Tyr	Gln	Gln 185	Asn		Pro	Ile	Gly 190	Asp	Gly	
	Pro	Val	Leu 195		Pro	Asp	Asn	His 200	Tyr		Ser	Thr	Gln 205	Ser		Leu	
50	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg		His	Met	Val 220	Leu		Glu	Phe	
		Thr		Ala	Gly		Thr		Gly	Met		Glu		Туг	Lys	Ser 240	
	225 Gly		Arg	Ser	Arg 245			Met	: Ala	Ala 250			Ala	Ala	Gly 255	Pro	
55	Glu	. Met	Val	Arg 260	Gly		. Val	. Phe	Asp 265	Val		Pro	Arg	Tyr 270	Thr	Asn	

75

	Leu	Ser	Tyr 275	Ile	Gly	Glu	Gly	Ala 280	Tyr	Gly	Met	Val	Cys 285	Ser	Ala	Tyr
	Asp	Asn 290	Leu	Asn	Lys	Val	Arg 295	Val	Ala	Ile	Lys	Lys 300	Ile	Ser	Pro	Phe
5	Glu 305	His	Gln	Thr	Tyr	Cys 310		Arg	Thr	Leu	Arg 315		Ile	Lys	Ile	Leu 320
	Leu	Arg	Phe	Arg	His 325		Asn	Ile	Ile	Gly 330		Asn	Asp	Ile	Ile 335	
10	Ala	Pro	Thr	Ile 340		Gln	Met	Lys	Asp		Tyr	Ile	Val	Gln 350		Leu
	Met	Glu	Thr 355		Leu	Tyr	Lys	Leu 360	Leu	Lys	Thr	Gln	His 365		Ser	Asn
	Asp	His 370		Сув	Tyr	Phe	Leu 375		Gln	Ile	Leu	Arg 380		Leu	Lys	Tyr
15	Ile 385		Ser	Ala	Asn	Val 390		His	Arg	Asp	Leu 395		Pro	Ser		Leu 400
		Leu	Asn	Thr	Thr		Asp	Leu	Lys	Ile 410		Asp	Phe	Gly		
20	Arg	Val	Ala	Asp		Asp	His	Asp	His		Gly	Phe	Leu	Thr		Tyr
20	Val	Ala	Thr 435		Trp	Tyr	Arg	Ala 440	Pro	Glu	Ile	Met	Leu 445		Ser	Lys
	Gly	Tyr 450		Lys	Ser	Ile	Asp		Trp	Ser	Val	Gly 460		Ile	Leu	Ala
25	Glu 465		Leu	Ser	Asn	Arg		Ile	Phe	Pro	Gly 475		His	Tyr	Leu	Asp
		Leu	Asn	His	Ile 485	_	Gly	Ile	Leu	Gly 490		Pro	Ser	Gln	Glu 495	
30	Leu	Asn	Cys	Ile 500		Asn	Leu	Lys	Ala 505		Asn	Tyr	Leu	Leu 510		Leu
	Pro	His	Lys 515		Lys	Val	Pro	Trp 520	Asn	Arg	Leu	Phe	Pro 525		Ala	Asp
	Ser	Lys 530		Leu	Asp	Leu	Leu 535		Lys	Met	Leu	Thr 540		Asn	Pro	His
35	Lys 545		Ile	Glu	Val	Glu 550		Ala	Leu	Ala	His 555		Tyr	Leu	Glu	Gln 560
		Tyr	Asp	Pro	Ser 565		Glu	Pro	Ile	Ala 570		Ala	Pro	Phe	Lys 575	
40	Asp	Met	Glu	Leu 580	Asp	Asp	Leu	Pro	Lys 585	Glu	Lys	Leu	Lys	Glu 590	Leu	Ile
	Phe	Glu	Glu 595	Thr	Ala	Arg	Phe	Gln 600	Pro	Gly	Tyr	Arg	Ser 605			
			(2	) IN	FORM	ATIO:	N FO	R SE	Q ID	NO:	42:					
45																
		(	i) S! (A)	_					ICS: airs							
				TYP												
50				STR TOP				_	e							
		(	ii)	MOLE	CULE	TYP	E: c	DNA								
		(	ix)	FEAT	URE:											

75

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...2526

# (D) OTHER INFORMATION:

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

	•-							-							
5	GTG Val												_		48
10	GAG Glu														96
15	GGC Gly													_	144
	ACC Thr 50														192
20	ACC Thr														240
25	CAC His														288
30	ACC Thr														336
35	AAG Lys														384
40	GAC Asp 130					Asn					Lys				432
40	-				Val					Asp		_		AAC Asn 160	480
45	ATC			Phe					Asn						528
50			Asp					ı Asr					Asp	GGC Gly	576
55		Leu					з Туг					ı Ser		CTG Leu	624

										,,							
					AAC Asn												672
5	GTG Val 225	ACC Thr	GCC Ala	GCC Ala	GGG Gly	ATC Ile 230	ACT Thr	CTC Leu	GGC Gly	ATG Met	GAC Asp 235	GAG Glu	CTG Leu	TAC Tyr	AAG Lys	TCC Ser 240	720
10	GGA Gly	CTC	AGA Arg	TCT Ser	CGA Arg 245	GCT Ala	CAA Gln	GCT Ala	TCG Ser	AAT Asn 250	TCG Ser	TCA Ser	ATG Met	GAG Glu	CTG Leu 255	GAA Glu	768
15					AAC Asn												816
20					GGG Gly												864
	CCT Pro	CAC His 290	ATT Ile	AGC Ser	CAG Gln	TGT Cys	GAA Glu 295	GAC Asp	CTC Leu	CGA Arg	AGG Arg	ACC Thr 300	ATA Ile	GAC Asp	AGA Arg	GAT Asp	912
25	TAC Tyr 305	TGC Cys	AGT Ser	TTA Leu	TGT Cys	GAC Asp 310	AAG Lys	CAG Gln	CCA Pro	ATC Ile	GGG Gly 315	AGG Arg	CTG Leu	CTT Leu	TTC Phe	CGG Arg 320	960
30	CAG Gln	TTT Phe	TGT Cys	GAA Glu	ACC Thr 325	AGG Arg	CCT Pro	GGG Gly	CTG Leu	GAG Glu 330	TGT Cys	TAC Tyr	ATT Ile	CAG Gln	TTC Phe 335	CTG Leu	1008
35	GAC Asp	TCC Ser	GTG Val	GCA Ala 340	GAA Glu	TAT Tyr	GAA Glu	GTT Val	ACT Thr 345	CCA Pro	GAT Asp	GAA Glu	AAA Lys	CTG Leu 350	GGA Gly	GAG Glu	1056
40	AAA Lys	GGG Gly	AAG Lys 355	GAA Glu	ATT Ile	ATG Met	ACC Thr	AAG Lys 360	TAC Tyr	CTC Leu	ACC Thr	CCA Pro	AAG Lys 365	TCC Ser	CCT Pro	GTT Val	1104
	TTC Phe	ATA Ile 370	GCC Ala	CAA Gln	GTT Val	GGC Gly	CAA Gln 375	GAC Asp	CTG Leu	GTC Val	TCC Ser	CAG Gln 380	ACG Thr	GAG Glu	GAG Glu	AAG Lys	1152
45	CTC Leu 385	CTA Leu	CAG Gln	AAG Lys	CCG Pro	TGC Cys 390	AAA Lys	GAA Glu	CTC Leu	TTT Phe	TCT Ser 395	GCC Ala	TGT Cys	GCA Ala	CAG Gln	TCT Ser 400	1200
50	GTC Val	CAC His	GAG Glu	TAC Tyr	CTG Leu 405	AGG Arg	GGA Gly	GAA Glu	CCA Pro	TTC Phe 410	CAC His	GAA Glu	TAT Tyr	CTG Leu	GAC Asp 415	AGC Ser	1248
55	ATG Met	TTT Phe	TTT Phe	GAC Asp 420	CGC Arg	TTT Phe	CTC Leu	CAG Gln	TGG Trp 425	AAG Lys	TGG Trp	TTG Leu	GAA Glu	AGG Arg 430	CAA Gln	CCG Pro	1296

		AAA Lys 435											1344
5		GAG Glu											1392
10		AAG Lys											1440
15		GCC Ala										_	1488
20		GTC Val											1536
20		CTG Leu 515									_		1584
25		GGC Gly						 				_	1632
30		ATC Ile										_	1680
35		GAT Asp									_		1728
40		ATC Ile											1776
40		CGC Arg 595					Val						1824
45						Leu				Trp		GGC	1872
50	Leu				Ile				Pro			CGT Arg 640	1920
55				Arg				Arg				ACG Thr	1968

	GAG Glu												2016
5	ATG Met												2064
10	GGG Gly 690												2112
15	AAG Lys												2160
20	CGC Arg												2208
20	GTG Val												2256
25	TTC Phe												2304
30	ACA Thr 770												2352
35	CCG Pro												2400
40	CTG Leu												2448
40	TCG Ser												2496
45	GTC Val									TAG			2529
50	( -							) ID	NO:4	13:			·
	1.2	.,	EQUE	ver (	-UMK	70151	TOL	LCD:					

- (A) LENGTH: 842 amino acids
- (B) TYPE: amino acid
- 55 (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

5		()	ci) S	EQUE	ENCE	DESC	RIPT	: NOI	SEC	] ID	NO:4	3:				
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Va?	Pro	Ile 15	Leu
10	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	_	50		Gly	_		55			_		60				
15	65			Gly		70					75					80
				Phe	85					90					95	
20				Phe 100					105					110		
		-	115	Glu	_	_		120			_		125		_	_
0.5		130		Lys			135				-	140	_			
25	145			Ser		150		_			155	_	-		_	160
				Val	165					170					175	
30				Ala 180	_		_		185					190		_
			195	Leu				200					205			
0.5		210	-	Pro			215	_	_			220				
35	225			Ala		230					235					240
	•		_	Ser	245					250					255	_
40				Ala 260					265	-		_		270	_	
			275	Lys				280	_		-		285			
4 ==		290		Ser		_	295	-		_		300		_		_
45	305			Leu		310					315					320
				Glu	325					330					335	
50	Asp	ser	val	A1a 340		туr	Glu	. val	Thr 345		Asp	Glu	гуз	150	_	Glu

80

400

Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro Lys Ser Pro Val

Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln Thr Glu Glu Lys

Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala Cys Ala Gln Ser

365

380

395

360

375

390

55

385

		** * _	~ 7	_		_	~		_							
			Glu		405					410					415	
	Met	Phe	Phe	Asp 420	Arg	Phe	Leu	Gln	Trp 425	Lys	Trp	Leu	Glu	Arg 430	Gln	Pro
5	Val	Thr	Lys 435	Asn	Thr	Phe	Arg	Gln 440	Tyr	Arg	Val	Leu	Gly 445	Lys	Gly	Gly
	Phe	Gly 450	Glu	Val	Cys	Ala	Cys 455	Gln	Val	Arg	Ala	Thr 460	Gly	Lys	Met	Туг
10	Ala 465		Lys	Arg	Leu	Glu 470	Lys	Lys	Arg	Ile	Lys 475	Lys	Arg	Lys	Gly	Glu 480
	Ser	Met	Ala	Leu	Asn 485	Glu	Lys	Gln	Ile	Leu 490		Lys	Val	Asn	Ser 495	
	Phe	Val	Val	Asn 500	Leu	Ala	Tyr	Ala	Tyr 505		Thr	Lys	Asp	Ala 510		Cys
15	Leu	Val	Leu 515	Thr	Ile	Met	Asn	Gly 520		Asp	Leu	Lys	Phe 525		Ile	Tyr
	Asn	Met 530	Gly	Asn	Pro	Gly	Phe 535		Glu	Glu	Arg	Ala 540		Phe	Tyr	Ala
	Ala		Ile	Leu	Cys	Gly		Glu	Asp	Leu	His		Glu	Asn	Thr	Val
20	545					550					555					560
	Tyr	Arg	Asp	Leu		Pro	Glu	Asn	Ile		Leu	Asp	Asp	Tyr	_	His
	Tle	Δνα	Ile	Ser	565	T.011	Glv.	T An	ת ז ת	570	T	т1-	Dwa	<b>~1</b>	575	7 ~~
	110	Arg	110	580	Asp	ьец	GIY	neu	585	Val	гÀг	TTE	PIO	590	GIY	ASL
25	Leu	Ile	Arg 595	Gly	Arg	Val	Gly	Thr 600	Val	Gly	Tyr	Met	Ala 605		Glu	Val
	Leu	Asn 610	Asn	Gln	Arg	Tyr	Gly 615	Leu	Ser	Pro	Asp	Tyr 620	Trp	Gly	Leu	Gly
30	Cys 625	Leu	Ile	Tyr	Glu	Met 630	Ile	Glu	Gly	Gln	Ser 635	Pro	Phe	Arg	Gly	Arc
	Lys	Glu	Lys	Val	Lys 645	Arg	Glu	Glu	Val	Asp 650	Arg	Arg	Val	Leu	Glu 655	
	Glu	Glu	Val	Tyr 660	Ser	His	Lys	Phe	Ser 665	Glu	Glu	Ala	Lys	Ser 670	Ile	Суз
35	Lys	Met	Leu 675	Leu	Thr	Lys	Asp	Ala 680	Lys	Gln	Arg	Leu	Gly 685	Cys	Gln	Glu
	Glu	Gly 690	Ala	Ala	Glu	Val	Lys 695	Arg	His	Pro	Phe	Phe 700	Arg	Asn	Met	Ası
40	Phe 705	Lys	Arg	Leu	Glu	Ala 710	Gly	Met	Leu	Asp	Pro 715	Pro	Phe	Val	Pro	Asp 720
	Pro	Arg	Ala	Val	Tyr 725	Cys	Lys	Asp	Val	Leu 730	Asp	Ile	Glu	Gln	Phe 735	Ser
	Thr	Val	Lys	Gly 740	Val	Asn	Leu	Asp	His 745	Thr	Asp	Asp	Asp	Phe 750	Tyr	Ser
45	Lys	Phe	Ser 755	Thr	Gly	Ser	Val	Ser 760	Ile	Pro	Trp	Gln	Asn 765	Glu	Met	Ile
	Glu	Thr 770	Glu	Cys	Phe	Lys	Glu 775	Leu	Asn	Val	Phe	Gly 780		Asn	Gly	Thr
50	Leu 785	Pro	Pro	Asp	Leu	Asn 790	Arg	Asn	His	Pro			Pro	Pro	Lys	
		Leu	Leu	Gln	Arg 805		Phe	Lys	Arg	Gln 810	795 His	Gln	Asn	Asn	Ser 815	B00 Lys
	Ser	Ser	Pro			Lys	Thr	Ser			His	His	Ile			Asr
55	His	Val	Ser	820 Ser	Asn	Ser	Thr	Gly	825 Ser	Ser				830		

		(2)	INF	ORMA	TION	FOR	SEÇ	DI	NO: 4	4:				
5	(i	(A) (B) (C)	QUEN LENG TYPE STRA	TH: E: nu	1902 Iclei NESS	bas c ac	e pa id ngle	irs						
10			OLEC		TYPE	: cI	NA							,
15	(c)	(B)	NAM LOC OTH	CATIO	N: 1 NFOR	I	.899 : MOI	-		NO : 4	4:			
20			AAG Lys											48
25			GAC Asp 20											96
20			GGC Gly											144
30			GGC Gly											192
35			GGC Gly											240
40			TTC Phe											288
45			TTC Phe 100											336
50			GAG Glu					Val						384
			AAG Lys				Asn							432
55			AGC										AAC	480

	145			150			155			160	
5			GTG Val								528
10			GCC Ala 180								576
			CTG Leu								624
15			CCC Pro								672
20			GCC Ala								720
25			TCT Ser		_	 					768 ·
30			TAT Tyr 260								816
00			CAG Gln								864
35			GCT Ala								912
40			CGA Arg								960
45			GTT Val			 					1008
<b>E</b> 0			GTT Val 340								1056
50			GTC Val								1104
55			CTA Leu								1152

CTG TGT GGA ATC AAG CAC CTT CAT TCT GCT GGA ATT ATT CAT CGG GAC Leu Cys Gly Ile Lys His Leu His Ser Ala Gly Ile Ile His Arg Asp TTA AAG CCC AGT AAT ATA GTA GTA AAA TCT GAT TGC ACT TTG AAG ATT Leu Lys Pro Ser Asn Ile Val Val Lys Ser Asp Cys Thr Leu Lys Ile CTT GAC TTC GGT CTG GCC AGG ACT GCA GGA ACG AGT TTT ATG ATG ACG Leu Asp Phe Gly Leu Ala Arg Thr Ala Gly Thr Ser Phe Met Met Thr CCT TAT GTA GTG ACT CGC TAC TAC AGA GCA CCC GAG GTC ATC CTT GGC Pro Tyr Val Val Thr Arg Tyr Tyr Arg Ala Pro Glu Val Ile Leu Gly ATG GGC TAC AAG GAA AAC GTG GAT TTA TGG TCT GTG GGG TGC ATT ATG Met Gly Tyr Lys Glu Asn Val Asp Leu Trp Ser Val Gly Cys Ile Met GGA GAA ATG GTT TGC CAC AAA ATC CTC TTT CCA GGA AGG GAC TAT ATT Gly Glu Met Val Cys His Lys Ile Leu Phe Pro Gly Arg Asp Tyr Ile GAT CAG TGG AAT AAA GTT ATT GAA CAG CTT GGA ACA CCA TGT CCT GAA Asp Gln Trp Asn Lys Val Ile Glu Gln Leu Gly Thr Pro Cys Pro Glu TTC ATG AAG AAA CTG CAA CCA ACA GTA AGG ACT TAC GTT GAA AAC AGA Phe Met Lys Lys Leu Gln Pro Thr Val Arg Thr Tyr Val Glu Asn Arg CCT AAA TAT GCT GGA TAT AGC TTT GAG AAA CTC TTC CCT GAT GTC CTT Pro Lys Tyr Ala Gly Tyr Ser Phe Glu Lys Leu Phe Pro Asp Val Leu TTC CCA GCT GAC TCA GAA CAC AAC AAA CTT AAA GCC AGT CAG GCA AGG Phe Pro Ala Asp Ser Glu His Asn Lys Leu Lys Ala Ser Gln Ala Arg GAT TTG TTA TCC AAA ATG CTG GTA ATA GAT GCA TCT AAA AGG ATC TCT Asp Leu Leu Ser Lys Met Leu Val Ile Asp Ala Ser Lys Arg Ile Ser GTA GAT GAA GCT CTC CAA CAC CCG TAC ATC AAT GTC TGG TAT GAT CCT Val Asp Glu Ala Leu Gln His Pro Tyr Ile Asn Val Trp Tyr Asp Pro TCT GAA GCA GAA GCT CCA CCA AAG ATC CCT GAC AAG CAG TTA GAT Ser Glu Ala Glu Ala Pro Pro Pro Lys Ile Pro Asp Lys Gln Leu Asp GAA AGG GAA CAC ACA ATA GAA GAG TGG AAA GAA TTG ATA TAT AAG GAA Glu Arq Glu His Thr Ile Glu Glu Trp Lys Glu Leu Ile Tyr Lys Glu

85

595 600 605 GTT ATG GAC TTG GAG GAG AGA ACC AAG AAT GGA GTT ATA CGG GGG CAG Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln 5 610 615 620 CCC TCT CCT TTA GCA CAG GTG CAG CAG TGA 1902 Pro Ser Pro Leu Ala Gln Val Gln Gln 630 10 (2) INFORMATION FOR SEQ ID NO:45: (i) SEQUENCE CHARACTERISTICS: 15 (A) LENGTH: 633 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45: 25 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 35 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 40 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 45 165 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 50 200 205 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 55 Gly Leu Arg Ser Arg Ala Arg Ala Ile Met Ser Arg Ser Lys Arg Asp

250

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Asn Asn Phe Tyr Ser Val Glu Ile Gly Asp Ser Thr Phe Thr Val Leu
                 260
                                     265
     Lys Arg Tyr Gln Asn Leu Lys Pro Ile Gly Ser Gly Ala Gln Gly Ile
                                 280
5
     Val Cys Ala Ala Tyr Asp Ala Ile Leu Glu Arg Asn Val Ala Ile Lys
                             295
                                                 300
     Lys Leu Ser Arg Pro Phe Gln Asn Gln Thr His Ala Lys Arg Ala Tyr
                         310
                                             315
     Arg Glu Leu Val Leu Met Lys Cys Val Asn His Lys Asn Ile Ile Gly
10
                      325
                                         330
     Leu Leu Asn Val Phe Thr Pro Gln Lys Ser Leu Glu Glu Phe Gln Asp
                                      345
     Val Tyr Ile Val Met Glu Leu Met Asp Ala Asn Leu Cys Gln Val Ile
                                  360
15
     Gln Met Glu Leu Asp His Glu Arg Met Ser Tyr Leu Leu Tyr Gln Met
                              375
                                                 380
     Leu Cys Gly Ile Lys His Leu His Ser Ala Gly Ile Ile His Arg Asp
                          390
                                             395
     Leu Lys Pro Ser Asn Ile Val Val Lys Ser Asp Cys Thr Leu Lys Ile
20
                      405
                                         410
     Leu Asp Phe Gly Leu Ala Arg Thr Ala Gly Thr Ser Phe Met Met Thr
                 420
                                      425
                                                         430
     Pro Tyr Val Val Thr Arg Tyr Tyr Arg Ala Pro Glu Val Ile Leu Gly
                                 440
25
     Met Gly Tyr Lys Glu Asn Val Asp Leu Trp Ser Val Gly Cys Ile Met
                             455
                                                 460
     Gly Glu Met Val Cys His Lys Ile Leu Phe Pro Gly Arg Asp Tyr Ile
                         470
                                              475
     Asp Gln Trp Asn Lys Val Ile Glu Gln Leu Gly Thr Pro Cys Pro Glu
30
                     485
                                         490
     Phe Met Lys Lys Leu Gln Pro Thr Val Arg Thr Tyr Val Glu Asn Arg
                 500
                                     505
     Pro Lys Tyr Ala Gly Tyr Ser Phe Glu Lys Leu Phe Pro Asp Val Leu
                                  520
35
     Phe Pro Ala Asp Ser Glu His Asn Lys Leu Lys Ala Ser Gln Ala Arg
                              535
     Asp Leu Leu Ser Lys Met Leu Val Ile Asp Ala Ser Lys Arg Ile Ser
                         550
                                              555
     Val Asp Glu Ala Leu Gln His Pro Tyr Ile Asn Val Trp Tyr Asp Pro
40
                      565
                                          570
     Ser Glu Ala Glu Ala Pro Pro Pro Lys Ile Pro Asp Lys Gln Leu Asp
                  580
                                      585
     Glu Arg Glu His Thr Ile Glu Glu Trp Lys Glu Leu Ile Tyr Lys Glu
                                 600
                                                      605
45
     Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln
                             615
     Pro Ser Pro Leu Ala Gln Val Gln Gln
                          630
               (2) INFORMATION FOR SEQ ID NO:46:
50
```

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1824 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

### (ii) MOLECULE TYPE: cDNA

#### (ix) FEATURE:

5 (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1821 (D) OTHER INFORMATION: (xi) SEQUENCE DESCRIPTION: SEO ID NO:46: 10 ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 15 GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144 20 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40 TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 30 CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 35 CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384 40 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 115 120 ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 45 130 AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 145 150 50

87

576

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC

Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly

170

165

88

								00					
			180				185				190		
5	 -								ACC Thr				624
10									GTC Val 220				672
									GAG Glu				720
15									AGG Arg				768
20									CCC Pro				816
25									TCT Ser				864
30									AAG Lys 300				912
50									TAC Tyr				960
35									GGT Gly				1008
40									GAT Asp				1056
45			Met						GTG Val		Cys	AAG Lys	1104
50		Asp				Phe				Ile		GGT Gly	1152
JU	 Lys				Ala				Arg			CCT Pro 400	1200
55												TTT Phe	1248

89

			405				410			415		
5		CGG Arg 420										1296
10		AGG Arg										1344
	 	GAT Asp	-					 				1392
15		ACA Thr										1440
20		AGA Arg										1488
25		GAG Glu 500										1536
30		AAC Asn									_	1584
30		CTG Leu										1632
35		CAA Gln										1680
40		GAA Glu										1728
45		CTT Leu 580	Ile				Ser					1776
50		GTG Val			-	Asp		 -	Glu			1824

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 607 amino acids

(B) TYPE: amino acid

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
  (v) FRAGMENT TYPE: internal
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

10	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
15	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	65		_	_		70	_			_	Tyr 75					80
20					85	_				90	Glu				95	
				100					105		Tyr			110		
		-	115		_	_		120			Arg		125			
25		130		_			135				Gly	140				
	145	_				150					Ala 155					160
30	_				165					170	Asn				175	
				180					185		Thr			190		
			195					200			Ser		205			
35		210					215				Met	220				
	225					230					Asp 235					240
40					245					250					255	_
	_			260		-			265		Val			270		
			275					280			Gly		285			
45		290					295				Val	300				
	305					310					315					Arg 320
50					325					330					335	
				340	1				345	5				350	·	Val
			355					360	)				365	5		Lys
55	Leu	370		Asp	His	. Val	. Glr 375		e Let	ı Ile	• Туг	380		e Leu	Arg	, Gly

	Leu 385	Lys	Tyr	Ile	His	Ser 390	Ala	Asp	Ile	Ile	His 395	Arg	Asp	Leu	Lys	Pro 400	
		Asn	Leu	Ala	Val		Glu	Asp	Cys	Glu		Lys	Ile	Leu	Asp		
_				_	405		_			410					415		
5	Gly	Leu	Ala	Arg 420	His	Thr	Asp	Asp	Glu 425	Met	Thr	Gly	Tyr	Val 430	Ala	Thr	
	Arg	Trp	Tyr 435		Ala	Pro	Glu	Ile 440	Met	Leu	Asn	Trp	Met 445		Tyr	Asn	
10	Gln	Thr 450		Asp	Ile	Trp	Ser 455		Gly	Cys	Ile	Met 460		Glu	Leu	Leu	
	Thr 465		Arg	Thr	Leu	Phe 470		Gly	Thr	qaA	His 475		Asp	Gln	Leu	Lys 480	
		Ile	Leu	Arg	Leu 485		Gly	Thr	Pro	Gly 490		Glu	Leu	Leu	Lys 495		
15	Ile	Ser	Ser	Glu 500		Ala	Arg	Asn	Tyr 505		Gln	Ser	Leu	Thr 510		Met	
	Pro	Lys	Met 515		Phe	Ala	Asn	Val 520	Phe	Ile	Gly	Ala	Asn 525		Leu	Ala	
20	Val			Leu	Glu	Lys			Val	Leu	Asp			Lys	Arg	Ile	
20		530 Ala	Ala	Gln	Ala		535 Ala	His	Ala	Tyr		540 Ala	Gln	Tyr	His	_	
	545 Pro	Asp	Asp	Glu		550 Val	Ala	Asp	Pro	Tyr 570	555 Asp	Gln	Ser	Phe		560 Ser	
25	Arg	qaA	Leu		565 Ile	Asp	Glu	Trp	Lys		Leu	Thr	Tyr	_	575 Glu	Val	
	Ile	Ser	Phe 595	580 Val	Pro	Pro	Pro	Leu 600	585 Asp	Gln	Glu	Glu	Met 605	590 Glu	Ser		
30				TNI	TORM!	וחדתב	v FOI		aı ç	NO · 4	18.		005				
00										110.			•				
		(:		-				RIST: se pa									
25					E: ni				_								
35					OLOG'			ingle r	2								
					CULE	TYP	E: cl	ANG									
40		١.	IX)	FEAT	JKE:												
					ME/KI CATIO				eque	nce							
					HER :												
45		(:	xi) :	SEQUI	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	48:					
	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	4.8
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
50	Cm.c	CAC	CTC	CAC	acc	CAC	CITIA	7 7 C	GGC	CAC	አአሮ	mmc.	אממ	CTC	TO C	ccc	96
									GGC Gly 25								30
55	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	144
	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	

		35			40				45			
5		ACC Thr										192
10		TAC Tyr										240
		GAC Asp										288
15		ATC Ile										336
20		TTC Phe 115										384
25		TTC Phe				 						432
30		AAC Asn										480
30		AAG Lys										528
35		CTC Leu										576
40		CTG Leu 195			His	 						624
45		GAC Asp							Leu			672
50	Thr	GCC Ala						Glu				720
50		AGA Arg		Ser			Gln				Tyr	768
55		AAA Lys										816

										~~							
				260					265					270			
5	ATA Ile	TTG Leu	ACT Thr 275	GTG Val	AAT Asn	AAA Lys	GGG Gly	TCC Ser 280	TTA Leu	GTA Val	GCT Ala	CTT Leu	GGA Gly 285	TTC Phe	AGT Ser	GAT Asp	864
10	GGA Gly	CAG Gln 290	GAA Glu	GCC Ala	AGG Arg	CCT Pro	GAA Glu 295	GAA Glu	ATT Ile	GGC Gly	TGG Trp	TTA Leu 300	AAT Asn	GGC Gly	TAT Tyr	AAT Asn	912
	GAA Glu 305	ACC Thr	ACA Thr	GGG Gly	GAA Glu	AGG Arg 310	GGG Gly	GAC Asp	TTT Phe	CCG Pro	GGA Gly 315	ACT Thr	TAC Tyr	GTA Val	GAA Glu	TAT Tyr 320	960
15	ATT Ile	GGA Gly	AGG Arg	AAA Lys	AAA Lys 325	ATC Ile	TCG Ser	CCT Pro	CCC Pro	ACA Thr 330	CCA Pro	AAG Lys	CCC Pro	CGG Arg	CCA Pro 335	CCT Pro	1008
20	CGG Arg	CCT Pro	CTT Leu	CCT Pro 340	GTT Val	GCA Ala	CCA Pro	GGT Gly	TCT Ser 345	TCG Ser	AAA Lys	ACT Thr	GAA Glu	GCA Ala 350	GAT Asp	GTT Val	1056
25	GAA Glu	CAA Gln	CAA Gln 355	GCT Ala	TTG Leu	ACT Thr	CTC Leu	CCG Pro 360	GAT Asp	CTT Leu	GCA Ala	GAG Glu	CAG Gln 365	TTT Phe	GCC Ala	CCT Pro	1104
30	CCT Pro	GAC Asp 370	ATT Ile	GCC Ala	CCG Pro	CCT Pro	CTT Leu 375	CTT Leu	ATC Ile	AAG Lys	CTC Leu	GTG Val 380	GAA Glu	GCC Ala	ATT Ile	GAA Glu	1152
	AAG Lys 385	AAA Lys	GGT Gly	CTG Leu	GAA Glu	TGT Cys 390	TCA Ser	ACT Thr	CTA Leu	TAC Tyr	AGA Arg 395	ACA Thr	CAG Gln	AGC Ser	TCC Ser	AGC Ser 400	1200
35	AAC Asn	CTG Leu	GCA Ala	GAA Glu	TTA Leu 405	CGA Arg	CAG Gln	CTT Leu	CTT Leu	GAT Asp 410	TGT Cys	GAT Asp	ACA Thr	CCC Pro	TCC Ser 415	GTG Val	1248
40	GAC Asp	TTG Leu	GAA Glu	ATG Met 420	ATC Ile	GAT Asp	GTG Val	CAC His	GTT Val 425	TTG Leu	GCT Ala	GAC Asp	GCT Ala	TTC Phe 430	AAA Lys	CGC Arg	1296
45	TAT Tyr	CTC Leu	CTG Leu 435	GAC Asp	TTA Leu	CCA Pro	AAT Asn	CCT Pro 440	GTC Val	ATT Ile	CCA Pro	GCA Ala	GCC Ala 445	GTT Val	TAC Tyr	AGT Ser	1344
50	GAA Glu	ATG Met 450	ATT Ile	TCT Ser	TTA Leu	GCT Ala	CCA Pro 455	GAA Glu	GTA Val	CAA Gln	AGC Ser	TCC Ser 460	GAA Glu	GAA Glu	TAT Tyr	ATT Ile	1392
	CAG Gln 465	CTA Leu	TTG Leu	AAG Lys	AAG Lys	CTT Leu 470	ATT Ile	AGG Arg	TCG Ser	CCT Pro	AGC Ser 475	ATA Ile	CCT Pro	CAT His	CAG Gln	TAT Tyr 480	1440
55	TGG Trp	CTT Leu	ACG Thr	CTT Leu	CAG Gln	TAT Tyr	TTG Leu	TTA Leu	AAA Lys	CAT His	TTC Phe	TTC Phe	AAG Lys	CTC Leu	TCT Ser	CAA Gln	1488

						04					
			485			490			495		
5							CTC Leu				1536
10							TCT Ser				1584
							ACT Thr 540				1632
15							CCA Pro				1680
20							TTA Leu				1728
25							AAT Asn				1776
30							GCG Ala				1824
							GGA Gly 620				1872
35							TTC Phe				1920
40							TAC Tyr				1968
45							TTA Leu				2016
50							GAT Asp				2064
		Lys				_	 TTT Phe 700	Gln			2112
55										GAA Glu	2160

	705				710				715				720	
5						GCT Ala						_		2208
10						CAG Gln								2256
		 				GAA Glu								2304
15						TTG Leu 775						_		2352
20		 				GAA Glu		-						2400
25						ATG Met							_	2448
30						CAA Gln							_	2496
30						AAC Asn							_	2544
35						GAA Glu 855						_		2592
40						GGA Gly								2640
45						GAT Asp							AGT Ser	2688
50				Tyr		TGC Cys						Val	AAG Lys	2736
50			Ile				Thr				Ala		CCC	2784
55													CAC His	2832

96

935 930 940 ACC TCC CTT GTG CAG CAC AAC GAC TCC CTC AAT GTC ACA CTA GCC TAC 2880 Thr Ser Leu Val Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr 5 950 955 CCA GTA TAT GCA CAG CAG AGG CGA TGA 2907 Pro Val Tyr Ala Gln Gln Arg Arg 965 10 (2) INFORMATION FOR SEQ ID NO:49: (i) SEQUENCE CHARACTERISTICS: 15 (A) LENGTH: 968 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein 20 (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49: 25 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 75 35 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 40 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 45 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 50 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 55 Gly Leu Arg Ser Met Ser Ala Glu Gly Tyr Gln Tyr Arg Ala Leu Tyr

96

250

	3		_	_		_	_									
				260					265					270		Asp
		Leu	275					280					285			
5	Gly	Gln 290	Glu	Ala	Arg	Pro	Glu 295	Glu	Ile	Gly	Trp	Leu 300	Asn	Gly	Tyr	Asn
	Glu 305	Thr	Thr	Gly	Glu	Arg 310	Gly	Asp	Phe	Pro	Gly 315	Thr	Tyr	Val	Glu	
10	Ile	Gly	Arg	Lys	Lys 325		Ser	Pro	Pro	Thr	Pro	Lys	Pro	Arg		320 Pro
	Arg	Pro	Leu	Pro 340	Val	Ala	Pro	Gly	Ser 345	Ser	Lys	Thr	Glu		335 Asp	Val
	Glu	Gln	Gln 355		Leu	Thr	Leu	Pro 360		Leu	Ala	Glu		350 Phe	Ala	Pro
15	Pro	Asp		Ala	Pro	Pro	Leu 375		Ile	Lys	Leu		365 Glu	Ala	Ile	Glu
	Lys 385	Lys	Gly	Leu	Glu	Cys 390		Thr	Leu	Tyr		380 Thr	Gln	Ser	Ser	
20		Leu	Ala	Glu	Leu 405		Gln	Leu	Leu		395 Cys	Asp	Thr	Pro		400 Val
	Asp	Leu	Glu	Met 420		Asp	Val	His	Val 425	410 Leu	Ala	Asp	Ala		415 Lys	Arg
	Tyr	Leu	Leu 435		Leu	Pro	Asn	Pro		Ile	Pro	Ala		430 Val	Tyr	Ser
25	Glu	Met 450		Ser	Leu	Ala	Pro 455		Val	Gln	Ser		445 Glu	Glu	Tyr	Ile
	Gln 465	Leu	Leu	Lys	Lys	Leu 470		Arg	Ser	Pro		460 Ile	Pro	His	Gln	
30		Leu	Thr	Leu	Gln 485		Leu	Leu	Lys		475 Phe	Phe	Lys	Leu		480 Gln
	Thr	Ser	Ser	Lys 500		Leu	Leu	Asn		490 Arg	Val	Leu	Ser		495 Ile	Phe
	Ser	Pro	Met 515		Phe	Arg	Phe	Ser 520	505 Ala	Ala	Ser	Ser		510 Asn	Thr	Glu
35	Asn	Leu 530		Lys	Val	Ile	Glu 535		Leu	Ile	Ser		525 Glu	Trp	Asn	Glu
	Arg 545	Gln	Pro	Ala	Pro	Ala 550		Pro	Pro	Lys		540 Pro	Lys	Pro	Thr	
40		Ala	Asn	Asn	Gly 565	Met	Asn	Asn	Asn		555 Ser	Leu	Gln	Asn		560 Glu
	Trp	Tyr	Trp				Ser	Arg	Glu	570 Glu	Val	Asn	Glu		575 Leu	Arg
	Asp	Thr	Ala 595		Gly	Thr	Phe		585 Val	Arg	Asp	Ala		590 Thr	Lys	Met
45	His	Gly 610		туг	Thr	Leu	Thr 615	600 Leu	Arg	Lys	Gly		605 Asn	Asn	Lys	Leu
	Ile 625	Lys	Ile	Phe	His	Arg 630		Gly	Lys	Tyr		620 Phe	Ser	Asp	Pro	
50		Phe	Ser	Ser	Val 645		Glu	Leu	Ile		635 His	Tyr	Arg	Asn		640 Ser
	Leu	Ala	Gln	Tyr 660		Pro	Lys	Leu		650 Val	Lys	Leu	Leu		655 Pro	Val
	Ser	Lys	Tyr 675		Gln	Asp	Gln	Val 680	665 Val	Lys	Glu	Asp		670 Ile	Glu	Ala
55	Val	Gly 690		Lys	Leu	His	Glu 695		Asn	Thr	Gln	Phe 700	685 Gln	Glu	Lys	Ser

	Arg 705	Glu	Tyr	Asp	Arg	Leu 710	Tyr	Glu	Glu	Tyr	Thr 715	Arg	Thr	Ser	Gln	Glu 720	
		Gln	Met	Lys	Arg 725	Thr	Ala	Ile	Glu	Ala 730	Phe	Asn	Glu	Thr	Ile 735	Lys	
5	Ile	Phe	Glu	Glu 740	Gln	Cys	Gln	Thr	Gln 745	Glu	Arg	Tyr	Ser	Lys 750	Glu	Tyr	
	Ile	G¹ u	Lys 755	Phe	Lys	Arg	Glu	Gly 760	Asn	Glu	Lys	Glu	Ile 765	Gln	Arg	Ile	
10	Met	His 770	Asn	Tyr	Asp	Lys	Leu 775	Lys	Ser	Arg	Ile	Ser 780	Glu	Ile	Ile	Asp	
	Ser 785	Arg	Arg	Arg	Leu	Glu 790	Glu	Asp	Leu	Lys	Lys 795	Gln	Ala	Ala	Glu	Tyr 800	
	Arg	Glu	Ile	Asp	Lys 805	Arg	Met	Asn	Ser	Ile 810	Lys	Pro	Asp	Leu	Ile 815	Gln	
15	Leu	Arg	Lys	Thr 820	Arg	Asp	Gln	Tyr	Leu 825	Met	Trp	Leu	Thr	Gln 830	ГÀЗ	Gly	
	Val	Arg	Gln 835	Lys	Lys	Leu	Asn	Glu 840	Trp	Leu	Gly	Asn	Glu 845	Asn	Thr	Glu	
20	Asp	Gln 850	Tyr	Ser	Leu	Val	Glu 855	Asp	Asp	Glu	Asp	Leu 860	Pro	His	His	Asp	
	Glu 865	Lys	Thr	Trp	Asn	Val 870	Gly	Ser	Ser	Asn	Arg 875	Asn	Lys	Ala	Glu	Asn 880	
	Leu	Leu	Arg	Gly	Lys 885	Arg	Asp	Gly	Thr	Phe 890	Leu	Val	Arg	Glu	Ser 895	Ser	
25	Lys	Gln	Gly	Cys 900	-	Ala	Сув	Ser	Val 905	Val	Val	Asp	Gly	Glu 910	Val	Lys	
	His	ĊAa	Val 915	Ile	Asn	Lys	Thr	Ala 920	Thr	Gly	Tyr	Gly	Phe 925	Ala	Glu	Pro	
30	Tyr	Asn 930	Leu	Tyr	Ser	Ser	Leu 935	_	Glu	Leu	Val	Leu 940		Tyr	Gln	His	
	Thr 945	Ser	Leu	Val	Gln	His 950		Asp	Ser	Leu	Asn 955		Thr	Leu	Ala	Tyr 960	
	Pro	Val	Tyr	Ala	Gln 965	Gln	Arg	Arg									
35			(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	50:						
		(	i) S	EQUE	NCE	CHAR	ACTE	RIST	ics:								
40					GTH: E: n				airs								
					ANDE OLOG			_	е								
		(	ii)	MOLE	CULE	TYP	E: 0	DNA									
45		(			URE:												
			(B	) LC	ME/K CATI	ON:	1	2157	,	ence							
50		_			HER												
										EQ II							
	Met				Gly					E Thi					) Ile	: CTG : Leu	48
55	1				5					10					15		

			GAC Asp						96
5			GCC Ala						144
10			CTG Leu						192
15			CAG Gln 70						240
20			AAG Lys						288
			AAG Lys						336
25			GAC Asp						384
30			GAC Asp						432
35			AAC Asn 150						480
40			TTC Phe						528
			CAC His						576
45			GAC Asp						624
50			GAG Glu						672
55			ATC Ile 230						720

							.00						
											TCC Ser 255		768
5											AAG Lys		816
10											GGG Gly		864
15											AAG Lys		912
00											ACT Thr		960
20											GAA Glu 335		1008
25											ACA Thr		1056
30											CTC Leu		1104
35											TTA Leu		1152
40											GAA Glu		1200
40											AAC Asn 415		1248
45											TTA Leu		1296
50						Glu				Asp		TAT Tyr	1344
55		Ser			Thr				Gly			CCA Pro	1392

						CCT Pro 475				1440
5						CAA Gln				1488
10						TCC Ser				1536
15						CCT Pro				1584
20						GGA Gly				1632
						ACA Thr 555				1680
25						GTT Val				1728
30						GGA Gly				1776
35						AGT Ser				1824
40						GGC Gly				1872
	_					AAG Lys 635				1920
45						AAT Asn				1968
50						AGA Arg				2016
55						GTA Val		Thr		2064

102

TGG ATT GAA CTT CAT CTG AAT GGA CCT CTA CAG TGG TTG GAC AAA GTA 2112 Trp Ile Glu Leu His Leu Asn Gly Pro Leu Gln Trp Leu Asp Lys Val 695 TTA ACT CAG ATG GGA TCC CCT TCA GTG CGT TGC TCA AGC ATG TCA TAA 5 2160 Leu Thr Gln Met Gly Ser Pro Ser Val Arg Cys Ser Ser Met Ser 705 710 715 10 (2) INFORMATION FOR SEQ ID NO:51: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 719 amino acids (B) TYPE: amino acid 15 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 25 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 30 55 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 75 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 35 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 40 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 45 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 205 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 50 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Ser Ser Ile 250 55 Leu Pro Phe Thr Pro Pro Val Val Lys Arg Leu Leu Gly Trp Lys Lys 265

	Ser	Ala	Gly 275	Gly	Ser	Gly	Gly	Ala 280	Gly	Gly	Gly	Glu	Gln 285	Asn	Gly	Gln
	Glu	Glu 290	Lys	Trp	Cys	Glu	Lys 295	Ala	Val	Lys	Ser	Leu 300	Val	Lys	Lys	Leu
5	Lys 305	Lys	Thr	Gly	Arg	Leu 310	Asp	Glu	Leu	Glu	Lys 315	Ala	Ile	Thr	Thr	Gln 320
	Asn	Cys	Asn	Thr	Lys 325	Cys	Val	Thr	Ile	Pro 330	Ser	Thr	Cys	Ser	Glu 335	Ile
10	Trp	Gly	Leu	Ser 340	Thr	Pro	Asn	Thr	Ile 345	Asp	Gln	Trp	Asp	Thr 350	Thr	Gly
	Leu	Tyr	Ser 355	Phe	Ser	Glu	Gln	Thr 360	Arg	Ser	Leu	Asp	Gly 365	Arg	Leu	Gln
	Val	Ser 370	His	Arg	Lys	Gly	Leu 375	Pro	His	Val	Ile	Tyr 380	Cys	Arg	Leu	Trp
15	Arg 385	Trp	Pro	Asp	Leu	His 390	Ser	His	His	Glu	Leu 395	Lys	Ala	Ile	Glu	Asn 400
	Cys	Glu	Tyr	Ala	Phe 405	Asn	Leu	Lys	Lys	Asp 410	Glu	Val	Cys	Val	Asn 415	Pro
20	Tyr	His	Tyr	Gln 420	Arg	Val	Glu	Thr	Pro 425	Val	Leu	Pro	Pro	Val 430	Leu	Val
	Pro	Arg	His 435	Thr	Glu	Ile	Leu	Thr 440	Glu	Leu	Pro	Pro	Leu 445	Asp	Asp	Tyr
	Thr	His 450	Ser	Ile	Pro	Glu	Asn 455	Thr	Asn	Phe	Pro	Ala 460	Gly	Ile	Glu	Pro
25	Gln 465	Ser	Asn	Tyr	Ile	Pro 470	Glu	Thr	Pro	Pro	Pro 475	Gly	Tyr	Ile	Ser	Glu 480
	Asp	Gly	Glu	Thr	Ser 485	Asp	Gln	Gln	Leu	Asn 490	Gln	Ser	Met	Asp	Thr 495	Gly
30	Ser	Pro	Ala	Glu 500	Leu	Ser	Pro	Thr	Thr 505	Leu	Ser	Pro	Val	Asn 510	His	Ser
	Leu	qaA	Leu 515	Gln	Pro	Val	Thr	Tyr 520	Ser	Glu	Pro	Ala	Phe 525	Trp	Cys	Ser
		530	Tyr				535				_	540				
35	545		Pro			550					555					560
			Phe		565					570					575	
40			Met	580					585		_		_	590	_	_
			Gly 595					600					605			
		610	Ser				615					620				
45	625		Lys			630					635					640
			Ala		645					650					655	
50			Gln	660					665					670		
			Gly 675					680					685			
		690	Glu				695					700				Val
55	Leu 705	Thr	Gln	Met	Gly	Ser 710	Pro	Ser	Val	Arg	Cys 715	Ser	Ser	Met	Ser	

### (2) INFORMATION FOR SEQ ID NO:52:

5	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 2421 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: cDNA</li> </ul>																
10		-	i) M lx) E			TYPE	E: cI	NA									
15			(B)	roc	CATIO	EY: C ON: 1 INFOR	L2	418	equer	ıce							
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG  48																
20														CCC Pro			48
25														GTG Val 30			96
30														AAG Lys			144
30														GTG Val			192
35														CAC His			240
40														GTC Val			288
45		ACC Thr												CGC Arg 110			336
50														CTG Leu			384
50			Phe					Asn						CTG Leu			432
55														CAG Gln			480

	145				150				155			160	
5										GAG Glu			528
10										ATC Ile			576
.0										CAG Gln 205	_		624
15										CTG Leu			672
20										CTG Leu			720
25		 			-	 				TCA Ser			768
30										GCC Ala			816
30										GAG Glu 285			864
35										CTG Leu	_	AAA Lys	912
40										ACA Thr			960
45									Thr	GAT Asp			1008
<b>5</b> 0				Arg				His			Arg	CTC Leu	1056
50			Pro				Asn					TAT	1104
55												CCA Pro	1152

	370				375				380				
5				GTT Val 390									1200
10				GCT Ala									1248
				GGA Gly							_		1296
15				CAT His									1344
20	 	 		CTG Leu									1392
25				AAC Asn 470									1440
30				AGC Ser									1488
				CAG Gln								_	1536
35	 _			AGC Ser									1584
40				TTG Leu								_	1632
45	Pro			CCC Pro 550					Trp				1680
50	 _	 		CCT Pro		 		His				Tyr	1728
50			Ala	TAC Tyr			Asp				Glu	ACA Thr	1776
55				AGC Ser								GTG Val	1824

107

			595					600					605				
5									TGT Cys								1872
10	CAC His 625	AGG Arg	ACA Thr	GAA Glu	GCC Ala	ATT Ile 630	GAG Glu	AGA Arg	GCA Ala	AGG Arg	TTG Leu 635	CAC His	ATA Ile	GGC Gly	AAA Lys	GGT Gly 640	1920
	GTG Val	CAG Gln	TTG Leu	GAA Glu	TGT Cys 645	AAA Lys	GGT Gly	GAA Glu	GGT Gly	GAT Asp 650	GTT Val	TGG Trp	GTC Val	AGG Arg	TGC Cys 655	CTT Leu	1968
15									AGT Ser 665								2016
20									CAT His								2064
25									TGT Cys								2112
30									GCT Ala								2160
									GTA Val								2208
35									GGT Gly 745								2256
40									AAA Lys								2304
45	AGA Arg	CAG Gln 770	AGC Ser	ATC Ile	AAA Lys	GAA Glu	ACA Thr 775	CCT Pro	TGC Cys	TGG Trp	ATT Ile	GAA Glu 780	ATT Ile	CAC His	TTA Leu	CAC His	2352
50	CGG Arg 785	GCC Ala	CTC Leu	CAG Gln	CTC Leu	CTA Leu 790	GAC Asp	GAA Glu	GTA Val	CTT Leu	CAT His 795	ACC Thr	ATG Met	CCG Pro	ATT Ile	GCA Ala 800	2400
					TTA Leu 805		TGA										2421

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 806 amino acids
              (B) TYPE: amino acid
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              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
10
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
15
      Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
                                      25
     Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
                                  40
      Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
20
                              55
      Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                          70
      Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                      85
                                          90
25
      Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
                                      105
      Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
      Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
30
                              135
      Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                          150
                                              155
      Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                                          170
35
      Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
                                      185
      Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
40
                              215
                                                  220
      Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                              235
      Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Asn Ser Thr Met Asp
                       245
                                          250
45
      Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys Leu Ser
                                       265
      Ile Val His Ser Leu Met Cys His Arg Gln Gly Gly Glu Ser Glu Thr
                                   280
      Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys Glu Lys
50
                               295
                                                   300
      Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn Gly Ala
                           310
                                              315
      His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly Arg Leu
                       325
                                          330
55
      Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala Arg Leu
                                       345
```

	Trp	Arg	Trp 355	Pro	Asp	Leu	His	Lys 360	Asn	Glu	Leu	Lys	His 365	Val	Lys	Tyr
	Cys	Gln 370	Tyr	Ala	Phe	Asp	Leu 375	Lys	Cys	Asp	Ser	Val 380	Cys	Val	Asn	Pro
5	Tyr 385	His	Tyr	Glu	Arg	Val 390	Val	Ser	Pro	Gly	Ile 395	Asp	Leu	Ser	Gly	Leu 400
					405					410				Asp	415	
10				420					425					Gly 430		
			435					440					445	Thr		
15		450					455					460		Ala		
15	465					470					475			Gln		480
				_	485					490				Ile	495	
20				500					505					Gln 510 Arg		
			515					520					525	Leu		
25		530					535		•			540		Val		
20	545					550					555			Pro		560
					565					570				Gly	575	_
30				580					585	_				590 Gly		
			595				•	600					605	Ser	_	
35		610					615		_			620		Gly		
	625					630				-	635			Arg		640
					645					650				Arg	655	
40				660					665					670 Ser		
			675					680					685	Gln		
45		690					695					700		Ala		
	705					710					715			Pro		720
	Ser	Leu	Ser	Ala	725 Ala	Ala	Gly	Ile	Gly	730 Val	Asp	Asp	Leu	Arg	735 Arg	Leu
50	Cys	Ile	Leu	740 Arg	Met	Ser	Phe	Val	745 Lys	Gly	Trp	Gly	Pro	750 Asp	Tyr	Pro
			755					760					765	His		
55		770					775		_			780		Pro		
	785					790	_				795					800

110

Asp Pro Gln Pro Leu Asp 805

5		(2)	INF	ORMA	TION	FOR	SEÇ	ID	NO : 5	4:				
	(i	(A) (B)	EQUEN LENG TYPE STRA	TH: E: nu	3120 clei	bas c ac	e pa	irs						
10		(D)	TOPO	LOGY	: li	near	•							
			OLEC		TYPE	: cI	AN							
15		(B)	LOC OTH	CATIC	N: 1	3	117	equen	ice					
20	()	ci) S	EQUE	ENCE	DESC	RIPI	: NOI	SEC	) ID	NO : 5	54:			
			AAG Lys											48
25			GAC Asp 20											96
30			Gly											144
35			GGC Gly						-	-				192
40			GGC Gly											240
40			TTC Phe											288
45			TTC Phe 100											336
50			GAG Glu											384
55		Phe	AAG Lys				Asn							432

	AAC Asn 145	TAC Tyr	AAC Asn	AGC Ser	CAC His	AAC Asn 150	GTC Val	TAT Tyr	ATC Ile	ATG Met	GCC Ala 155	GAC Asp	AAG Lys	CAG Gln	AAG Lys	AAC Asn 160	480
5	GGC Gly	ATC Ile	AAG Lys	GTG Val	AAC Asn 165	TTC Phe	AAG Lys	ATC Ile	CGC Arg	CAC His 170	AAC Asn	ATC Ile	GAG Glu	GAC Asp	GGC Gly 175	AGC Ser	528
10	GTG Val	CAG Gln	CTC Leu	GCC Ala 180	GAC Asp	CAC His	TAC Tyr	CAG Gln	CAG Gln 185	AAC Asn	ACC Thr	CCC Pro	ATC Ile	GGC Gly 190	GAC Asp	GGC Gly	576
15	CCC Pro	GTG Val	CTG Leu 195	CTG Leu	CCC Pro	GAC Asp	AAC Asn	CAC His 200	TAC Tyr	CTG Leu	AGC Ser	ACC Thr	CAG Gln 205	TCC Ser	GCC Ala	CTG Leu	624
20	AGC Ser	AAA Lys 210	GAC Asp	CCC Pro	AAC Asn	GAG Glu	AAG Lys 215	CGC Arg	GAT Asp	CAC His	ATG Met	GTC Val 220	CTG Leu	CTG Leu	GAG Glu	TTC Phe	672
	GTG Val 225	ACC Thr	GCC Ala	GCC Ala	GGG Gly	ATC Ile 230	ACT Thr	CTC Leu	GGC Gly	ATG Met	GAC Asp 235	GAG Glu	CTG Leu	TAC Tyr	AAG Lys	TCC Ser 240	720
25	GGA Gly	CTC Leu	AGA Arg	TCT Ser	ACC Thr 245	ATG Met	GCG Ala	GGC Gly	TGG Trp	ATC Ile 250	CAG Gln	GCC Ala	CAG Gln	CAG Gln	CTG Leu 255	CAG Gln	768
30	GGA Gly	GAC Asp	GCG Ala	CTG Leu 260	CGC Arg	CAG Gln	ATG Met	CAG Gln	GTG Val 265	CTG Leu	TAC Tyr	GGC Gly	CAG Gln	CAC His 270	TTC Phe	CCC Pro	816
35	ATC Ile	GAG Glu	GTC Val 275	CGG Arg	CAC His	TAC Tyr	TTG Leu	GCC Ala 280	CAG Gln	TGG Trp	ATT Ile	GAG Glu	AGC Ser 285	CAG Gln	CCA Pro	TGG Trp	864
40	GAT Asp	GCC Ala 290	ATT Ile	GAC Asp	TTG Leu	GAC Asp	AAT Asn 295	CCC Pro	CAG Gln	GAC Asp	AGA Arg	GCC Ala 300	CAA Gln	GCC Ala	ACC Thr	CAG Gln	912
40	CTC Leu 305	CTG Leu	GAG Glu	GGC Gly	CTG Leu	GTG Val 310	CAG Gln	GAG Glu	CTG Leu	CAG Gln	AAG Lys 315	AAG Lys	GCG Ala	GAG Glu	CAC His	CAG Gln 320	960
45	GTG Val	GGG Gly	GAA Glu	GAT Asp	GGG Gly 325	TTT Phe	TTA Leu	CTG Leu	AAG Lys	ATC Ile 330	AAG Lys	CTG Leu	GGG Gly	CAC His	TAC Tyr 335	GCC Ala	1008
50	ACG Thr	CAG Gln	CTC Leu	CAG Gln 340	AAA Lys	ACA Thr	TAT Tyr	GAC Asp	CGC Arg 345	TGC Cys	CCC Pro	CTG Leu	GAG Glu	CTG Leu 350	GTC Val	CGC Arg	1056
55	TGC Cys	ATC Ile	CGG Arg 355	CAC His	ATT Ile	CTG Leu	TAC Tyr	AAT Asn 360	GAA Glu	CAG Gln	AGG Arg	CTG Leu	GTC Val 365	CGA Arg	GAA Glu	GCC Ala	1104

•																
			AGC Ser													1152
5			CAG Gln													1200
10			GAG Glu													1248
15			CAG Gln 420											_	_	1296
20			CAG Gln													1344
20			AAG Lys													1392
25			CAG Gln										_	_		1440
30			CTG Leu												_	1488
35			TGG Trp 500													1536
40								Gln					Lys		GCC Ala	1584
40		Ile					Gln					Ala			CTC Leu	1632
45	Gln					Pro					Glu				GAG Glu 560	1680
50					Thr					Ala					C ACA Thr	1728
55				Lys					ı Val					Thi	AAG Lys	1776

								113							
			ACC Thr												1824
5			CCC Pro											_	1872
10			CTT Leu												1920
15			AAC Asn												1968
			CAC His 660								_			_	2016
20			GGT Gly												2064
25			CAG Gln												2112
30	Thr		TCC Ser												2160
35			ACG Thr	Thr										Pro	2208
			CCA Pro 740										Gln	CTG Leu	2256
40			Leu				Lys					Ser		CGG Arg	2304
45	 	Thr				Val					Lys			AAC Asn	2352
50	ser				Glu					Leu				TGG Trp 800	2400
55				Glu					Trp					TGG Trp	2448

									1 14							
									TTG Leu							2496
5	 								TTT Phe							2544
10									GGG Gly							2592
15									ATC Ile							2640
									CCA Pro 890							2688
20	 								GGG Gly							2736
25	 		_						GAG Glu							2784
30									GGA Gly							2832
35									GCA Ala		Ala					2880
40					Met				CCC Pro 970	Ser					Pro	2928
40				Asn					Asn					Leu	GAT Asp	2976
45			Glu					Glu					. Ala		CAC His	3024
50		Glu					Pro					Asp			CTC Leu	3072
55	Pro					Phe			GCC Ala		g Gly				A TGA	3120

115

## (2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1039 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: protein

5

(v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

				-						_	-						
1	5	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
		Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
2	0		_	35					40	_	_	Leu		45	_		
		Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
		Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
2	5			-		85	_				90	Glu	_	•		95	
					100				_	105		Tyr	_		110		
3	0		_	115			_		120			Arg		125		-	_
		Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
		145	_				150		_			Ala 155	_	_		_	160
3:	5					165					170	Asn				175	
					180	_		_		185		Thr			190		_
4	0			195					200			Ser		205			
			210					215		_		Met	220				
	_	225				_	230			_		Asp 235			_	_	240
4	5					245					250	Gln				255	
					260					265		Tyr			270		
5	0	Ile	Glu	Val 275	Arg	His	Tyr	Leu	Ala 280	Gln	Trp	Ile	Glu	Ser 285	Gln	Pro	Trp
		_	290		_		•	295			-	Arg	300				
_	_	305					310					315					Gln 320
5	5	Val	Gly	Glu	Asp	Gly 325	Phe	Leu	Leu	Lys	11e 330	Lys	Leu	Gly	His	Tyr 335	Ala

	Thr	Gln	Leu		Lys	Thr	Tyr	Asp		Cys	Pro	Leu	Glu	Leu	Val	Arg
	Crea	770	71	340	77.0	T	///n	71	345	~ 1	_	_		350		
_			355					360					365	Arg		
5	Asn	Asn 370	Сув	Ser	Ser	Pro	Ala 375	Gly	Ile	Leu	Val	Asp 380	Ala	Met	Ser	Glr
	Lys 385	His	Leu	Gln	Ile	Asn 390	Gln	Thr	Phe	Glu	Glu 395	Leu	Arg	Leu	Val	Thr
		Asp	Thr	Glu	Asn		Leu	Lvs	Lvs	Leu		Gln	Thr	Gln	Glu	
10		-			405				1	410				0	415	-1-
	Phe	Ile	Ile	Gln 420	Tyr	Gln	Glu	Ser	Leu 425	Arg	Ile	Gln	Ala	Gln 430	Phe	Ala
	Gln	Leu	Ala 435	Gln	Leu	Ser	Pro	Gln 440	Glu	Arg	Leu	Ser	Arg	Glu	Thr	Ala
15	Leu	Gln 450		Lys	Gln	Val	Ser 455	_	Glu	Ala	Trp	Leu 460		Arg	Glu	Ala
	Gln 465		Leu	Gln	Gln	Tyr 470		Val	Glu	Leu			Lys	His	Gln	
		Leu	Gln	ĭ.e.ı	Len		Tare	GIn	Gln	Thr.	475	Tlo	T 011	Asp	7 ~~	480
20		204	<b></b>		485	m y	Lys	GIII	GIII	490	TIE	TTE	пеп	Asp	495	GIU
	Leu	Ile	Gln	Trp 500	Lys	Arg	Arg	Gln	Gln 505		Ala	Gly	Asn	Gly 510		Pro
	Pro	Glu	Gly 515	Ser	Leu	Asp	Val	Leu 520		Ser	Trp	Cys	Glu 525	Lys	Leu	Ala
25	Glu	Ile 530	Ile	Trp	Gln	Asn	Arg 535	Gln	Gln	Ile	Arg	Arg 540		Glu	His	Let
	Cys 545	Gln	Gln	Leu	Pro	Ile 550	Pro	Gly	Pro	Val	Glu 555		Met	Leu	Ala	Glu 560
30	Val	Asn	Ala	Thr	Ile 565		Asp	Ile	Ile	Ser 570		Leu	Val	Thr	Ser 575	
	Phe	Ile	Ile	Glu 580		Gln	Pro	Pro	Gln 585		Leu	Lys	Thr	Gln 590		Ьγε
	Phe	Ala	Ala		Val	Ara	Leu	Leu		Glv	Glv	Lvs	Leu	Asn	Val	His
			595					600		0-7	/	-,,-	605		***	****
35	Met	Asn 610	Pro	Pro	Gln	Val	Lys 615	Ala	Thr	Ile	Ile	Ser 620	Glu	Gln	Gln	Ala
	Lys 625	Ser	Leu	Leu	Lys	Asn 630	Glu	Asn	Thr	Arg	Asn 635		Cys	Ser	Gly	Glu 640
40	Ile	Leu	Asn	Asn	Cys 645		Val	Met	Glu	Tyr 650		Gln	Ala	Thr	Gly 655	
	Leu	Ser	Ala	His 660		Arg	Asn	Met	Ser 665		Lys	Arg	Ile	Lys 670		Ala
	Asp	Arg	Arg 675		Ala	Glu	Ser	Val 680		Glu	Glu	Lys		Thr	Val	Let
45	Phe	Glu 690		Gln	Phe	Ser			Ser	Asn	Glu		685 Val	Phe	Gln	Va]
	Lvs		Len	Ser	Len	Pro	695 Val	Va I	Val	Tla	1757	700	C111	Ser	C1 =	7 0 0
	705					710					715					720
50	urs	ASII	Ата	TILL	725	Inr	vai	ьеп	Trp	730	Asn	Ата	Pne	Ala		Pro
	Gly	Arg	Val	Pro		Ala	Val	Pro			Val	Leu	Trp	Pro	735 Gln	Lev
	Cys	Glu	Ala 755		Asn	Met	Lγs		745 Lys	Ala	Glu	Val		750 Ser	Asn	Arg
55	Gly	Leu 770	Thr	Lys	Glu	Asn	Leu 775		Phe	Leu	Ala	Gln		Leu	Phe	Ası

	Asn 785	Ser	Ser	Ser	His	Leu 790	Glu	Asp	Tyr	Ser	Gly 795	Leu	Ser	Val	Ser	Trp 800	
	Ser	Gln	Phe	Asn	Arg 805	Glu	Asn	Leu	Pro	Gly 810	Trp	Asn	Tyr	Thr	Phe 815	Trp	
5	Gln	Trp	Phe	Asp 820		Val	Met	Glu	Val 825		Lys	Lys	His	His 830		Pro	
	His	Trp	Asn 835		Gly	Ala	Ile	Leu 840		Phe	Val	naA	Lys 845		Gln	Ala	
10	His	Asp 850		Leu	Ile	Asn	Lys 855	Pro	Asp	Gly	Thr	Phe 860		Leu	Arg	Phe	
	Ser 865	Asp	Ser	Glu	Ile	Gly 870	Gly	Ile	Thr	Ile	Ala 875	Trp	Lys	Phe	Asp	Ser 880	
		Glu	Arg	Asn	Leu 885		Asn	Leu	Lys	Pro 890		Thr	Thr	Arg	Asp 895	Phe	
15	Ser	Ile	Arg	Ser 900	Leu	Ala	Asp	Arg	Leu 905		Asp	Leu	Ser	Tyr 910	Leu	Ile	
	Tyr	Val	Phe 915	Pro	Asp	Arg	Pro	Lys 920	Asp	Glu	Val	Phe	Ser 925	ГЛЗ	Tyr	Tyr	
20	Thr	Pro 930	Val	Leu	Ala	Lys	Ala 935	Val	Asp	Gly	Tyr	Val 940	Lys	Pro	Gln	Ile	
	Lys 945	Gln	Val	Val	Pro	Glu 950	Phe	Val	Asn	Ala	Ser 955	Ala	Asp	Ala	Gly	Gly 960	
		Ser	Ala	Thr	Tyr 965	Met	Asp	Gln	Ala	Pro 970		Pro	Ala	Val	Cys 975	Pro	
25	Gln	Ala	Pro	Tyr 980		Met	Tyr	Pro	Gln 985		Pro	Asp	His	Val 990		Asp	
	Gln	Asp	Gly 995		Phe	Asp		Asp		Thr	Met	Asp	Val		Arg	His	
30		Glu 1010	Glu	Leu	Leu		Arg	Pro	Met	Asp		Leu 1020	Asp	Ser	Arg	Leu	
	Ser 025	Pro	Pro	Ala	_	Leu 1030	Phe	Thr	Ser		Arg 1035	Gly	Ser	Leu		1	
35			(2)	INI	FORM	ATIO	v FO	R SE	Q ID	NO:	56:						
33		(:	i) SI	EQUEI LENG													
			(B)	TYP	E: n	ucle	ic a	cid									
40				TOP				_	=								
		•	ii) 1 ix) 1			TYP	E: c	DNA									
45			(B	) NAI	CATI	ON:	1	1872	eque	nce							
50		(:	xi) :	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	56:					
50												GGC					48
55							-					GAG Glu					96

PCT/DK98/00145 WO 98/45704

							•	118						
			20				25				30			
5	 		CCA Pro									_		144
			GGC Gly									_	_	192
10			AGA Arg								_		_	240
15			CAG Gln						_				_	288
20	 	-	AAT Asn 100										_	336
25			ATG Met											384
			AAG Lys									_	_	432
30			CTC Leu										TCA Ser 160	480
35			CTG Leu										AAC Asn	528
40			GAC Asp 180	Leu				Phe				Ile	GCT Ala	576
45			His				Phe				Val		ACA Thr	624
50		Tyr				Ile				Lys			ACC Thr	672
50	Ser				Ser				Lev	_			CTC Leu 240	720
55													AAC Asn	768

						113				
			245			250			255	
5								GAC Asp		816
10								CTG Leu 285		864
								GAC Asp		912
15								AAC Asn		960
20								CAG Gln		1008
25								TTC Phe		1056
30								ATC Ile 365		1104
								GGG Gly		1152
35								ATT Ile		1200
40								AGT Ser		1248
45								TTT Phe		1296
50								ACT Thr 445		1344
								ATG Met		1392
55								CAG Gln		1440

PCT/DK98/00145 WO 98/45704

									•	120								
	465					470					475					480		
5							GGG Gly											1488
40							GTT Val											1536
10							ATT Ile											1584
15							ATC Ile 535											1632
20							AGA Arg											1680
25	TTA Leu	GCA Ala	GAC Asp	CAT His	TAT Tyr 565	CAA Gln	CAA Gln	AAT Asn	ACT Thr	CCA Pro 570	ATT Ile	GGC Gly	GAT Asp	GGC Gly	CCT Pro 57 <b>5</b>	Val		1728
30	CTT Leu	TTA Leu	CCA Pro	GAC Asp 580	AAC Asn	CAT His	TAC Tyr	CTG Leu	TCC Ser 585	ACG Thr	CAA Gln	TCT	GCC Ala	CTT Leu 590	TCC Ser	AAA Lys		1776
30	GAT Asp	CCC Pro	AAC Asn 595	Glu	AAG Lys	AGA Arg	GAT Asp	CAC His 600	ATG Met	ATC	CTT Leu	CTT Leu	GAG Glu 605	Phe	GTA Val	ACA Thr		1824
35			Gly					Met					. Lys			GAG 1 Glu	Т	1873
40	AA		(2	ni (!	IFORM	OITA	N FO	R SE	Q II	O NO:	57:							1875
45		,	(A) (B) (C)	LEN TYP STF	IGTH: PE: a RANDE	624 minc DNES	ACTE ami aci SS: s	.no a .d :ingl	cids									
50			(v) 1	FRAGI	TNBN	TYPE	PE: p E: ir SCRII	iteri	nal	EQ II	ои с	:57:						
55	1				5					10					15	o Arg		1

				20					25					30		
			35		Phe			40					45			
5		50			Ala		55					60				
	65				Val	70					75					80
					Arg 85					90					95	
10				100	Val				105					110		
			115		Arg			120					125			
15		130			Leu		135					140				
	145				Tyr	150					155					160
20					His 165					170					175	
20				180	Leu				185					190		
			195		Asp			200					205			
25		210			Ala		215					220				
	225				Ile	230					235					240
30					Ile 245					250					255	
30				260	Ile				265					270		
			275		Lys			280					285			
35		290			Trp		295					300				
	305				Asp	310					315					320
40					Ala 325					330					335	
40				340	Pro				345					350		
			355		Pro			360					365			
45		370			Gln		375					380				
	385				Glu	390					395					400
50					Val 405					410					415	
50				420	Thr				425					430		
			435		Pro			440					445			
55		450			Cys		455					460				
	Hah	FIIE	FIIG	пÀг	Ser	нта	met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr

	465					470					475					480	
	Ile	Phe	Tyr	Lys	Asp 485	Asp	Gly	Asn	Tyr	Lys 490	Thr	Arg	Ala	Glu	Val 495	Lys	
5	Phe	Glu	Gly	Asp 500	Thr	Leu	Val	Asn	Arg 505	Ile	Glu	Leu	Lys	Gly 510	Ile	Asp	
	Phe	Lys	Glu 515	qaA	Gly	Asn	Ile	Leu 520	Gly	His	Lys	Met	Glu 525	Tyr	Asn	Tyr	
	Asn	Ser 530	His	Asn	Val	Tyr	Ile 535		Ala	Asp	Lys	Pro 540	Lys	Asn	Gly	Ile	
10	Lys 545		Asn	Phe	Lys	Ile 550	Arg	His	Asn	Ile	Lys 555	Asp	Gly	Ser	Val	Gln 560	
		Ala	Asp	His	Tyr 565		Gln	Asn	Thr	Pro 570	Ile	Gly	Asp	Gly	Pro 575	Val	
15	Leu	Leu	Pro	Asp 580		His	Tyr	Leu	Ser 585		Gln	Ser	Ala	Leu 590		Lys	
.0	Asp	Pro	Asn 595		Lys	Arg	qaA	His 600		Ile	Leu	Leu	Glu 605		Val	Thr	
	Ala	Ala 610		Ile	Thr	His	Gly 615		Asp	Glu	Leu	Tyr 620		Pro	Gln	Glu	
20		010	(2)	TNI	rago.	ו אדינ	N FOI	9 SE(	מד נ	MO·	5 Q .	020					
										NO.							
25		<b>(</b> )	(A) (B) (C)	LENC TYPI STRA	E: ni ANDE	181! icle: ONES!	ACTEI 5 bas ic ac 5: s: inea:	se pa cid ingle	airs								
30		_		OLEC FEAT		TYP	E: cì	ANC									
			(B)	) LO	CATI	ON:	Codi: 1 RMAT	1811	eque	nce							
35		(:	xi) :	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	58:					
	ATG	GCG	GCG	GCG	GCG	GCG	GCG	GGC	CCG	GAG	ATG	GTC	CGC	GGG	CAG	GTG	48
40	Met 1	Ala	Ala	Ala	Ala 5	Ala	Ala	Gly	Pro	Glu 10	Met	Val	Arg	Gly	Gln 15	Val	
																GGC Gly	96
45		кор	Val	20	110	nr 9	ryr	1111	25	ДСС	ber	171	110	30	010	027	
40																CGA	144
	AIa	TYL	35	Mec	vai	Cys	ser	40	Tyr	Asp	ASI	. Leu	45	пуъ	Val	Arg	
50																CAG	192
	val	50	тте	ьys	ъys	тте	55 55	PIC	PHE	. 610	n nie	60	111E	тÄГ	Сув	Gln	
55															_	AAC	240
JJ	65	LIII	nεα	. mrg	, GIU	70	. nys	. TTE	ישכנ	י הבר	75	, E116	- WIG	, 1112	, 516	Asn 80	

													CAG Gln 95		288
5													TAC Tyr		336
10													TTT Phe		384
15													GTT Val		432
20													TGT Cys		480
0.5													GAC Asp 175		528
25													TAC Tyr		576
30													ATT Ile		624
35		Ser											AGG Arg		672
40	Phe									Asn			CTG Leu	GGT Gly 240	720
4.5					Ser				Asn					TTA Leu	768
45				туг				Pro					. Val	CCG Pro	816
50			Leu				a Asp					ı Asp		CTG Leu	864
55		Met				Pro					e Gli			A CAG	. 912

5							CAG Gln								960
3							TTT Phe			_				_	1008
10							ATT Ile 345								1056
15							CCA Pro								1104
20							GTG Val								1152
25							TTC Phe						_	_	1200
							ACC Thr						_	_	1248
30							ACC Thr 425								1296
35							CCC Pro					Gln		GAC Asp	1344
40						Glu					Glu			ATC Ile	1392
45	Phe				Asn					Ala				TTC Phe 480	1440
43				Val					Leu					TTC Phe	1488
50			Asn					Lys					туг	AAC Asn	1536
55		ı Val					a Asp					a Gly	_	AAG Lys	1584

5	GTG Val	AAC Asn 530	TTC Phe	AAG Lys	ATC Ile	CGC Arg	CAC His 535	AAC Asn	ATC Ile	GAG Glu	GAC Asp	GGC Gly 540	AGC Ser	GTG Val	CAG Gln	CTC Leu	1632
	GCC Ala 545	GAC Asp	CAC His	TAC Tyr	CAG Gln	CAG Gln 550	AAC Asn	ACC Thr	CCC Pro	ATC Ile	GGC Gly 555	GAC Asp	GGC Gly	CCC Pro	GTG Val	CTG Leu 560	1680
10	CTG Leu	CCC Pro	GAC Asp	AAC Asn	CAC His 565	TAC Tyr	CTG Leu	AGC Ser	ACC Thr	CAG Gln 570	TCC Ser	GCC Ala	CTG Leu	AGC Ser	AAA Lys 575	GAC Asp	1728
15	CCC Pro	AAC Asn	GAG Glu	AAG Lys 580	CGC Arg	GAT Asp	CAC His	ATG Met	GTC Val 585	CTG Leu	CTG Leu	GAG Glu	TTC Phe	GTG Val 590	ACC Thr	GCC Ala	1776
20	GCC Ala	GGG Gly	ATC Ile 595	ACT Thr	CTC Leu	GGC Gly	ATG Met	GAC Asp 600	GAG Glu	CTG Leu	TAC Tyr	AA ( Lys	GTAA				1815
			(2)	IN	FORM	TIOI	V FOI	R SE(	Q ID	NO:!	59:						
25		(:	(A) (B) (C)	LENG TYPI STRA	STH: E: ar ANDEI	CHARA 604 nino NESS	amir acio 8: si	no ad i ingle	cids								
30		(7	ii) M 7) FF	MOLE (	CULE ENT 1	TYPE:	E: pi	rotei	al		<b>.</b>						
35	Mot												_	<b>~</b> 7			
	1				5					10			Arg Ile	_	15		
40				20					25				Asn	30		_	
			35					40					45 Thr				
		50					55					60	Arg				
45	65					70					75		Ile			80	
					85					90					95		
50				100					105				Asp	110			
50			115					120					Cys 125				
		130					135					140	Ala				
55	145					150					155		Thr			160	
	Leu	Lys	Ile	Cys	Asp	Phe	Gly	Leu	Ala	Arg	Val	Ala	Asp	Pro	qaA	His	

										120						
					165					170					175	
	Asp	His	Thr	Gly 180	Phe	Leu	Thr	Glu	Tyr 185	Val	Ala	Thr	Arg	Trp 190	Tyr	Arg
5	Ala	Pro	Glu 195	Ile	Met	Leu	Asn	Ser 200	Lys	Gly	Tyr	Thr	Lys 205	Ser	Ile	Asp
	Ile	Trp 210	Ser	Val	Gly	Cys	Ile 215	Leu	Ala	Glu	Met	Leu 220	Ser	Asn	Arg	Pro
	Ile 225	Phe	Pro	Gly	Lys	His 230	Tyr	Leu	Asp	Gln	Leu 235	Asn	His	Ile	Leu	Gly 240
10	Ile	Leu	Gly	Ser	Pro 245	Ser	Gln	Glu	Asp	Leu 250	Asn	Cys	Ile	Ile	Asn 255	Leu
	Lys	Ala	Arg	Asn 260	Tyr	Leu	Leu	Ser	Leu 265	Pro	His	Lys	Asn	Lys 270	Val	Pro
15	Trp	Asn	Arg 275	Leu	Phe	Pro	Asn	Ala 280	Asp	ser	Lys	Ala	Leu 285	Asp	Leu	Leu
	Asp	Lys 290	Met	Leu	Thr	Phe	Asn 295	Pro	His	Lys	Arg	Ile 300	Glu	Val	Glu	Gln
	305			His		310					315					320
20				Glu	325					330					335	
				Lys 340					345					350		
25			355	Tyr				360					365			
		370		Glu			375					380				
30	385			Val		390					395					400
30				Thr	405					410					415	
				Pro 420					425					430		
35			435	Cys				440					445			
		450		Ser			455					460				Phe
40	465			Thr		470					475					480
					485					490					495	Asn
				500 Val					505					510		
45			515					520					525			Leu
		530					535					540				Leu
50	545			Asn		550					555					560
					565					570					575	Ala
				580 Thr					585				- 410	590	****	AIG
55		-	595			4	<b>-</b>	600			-1~	-, <b>.</b>				

(2) INFORMATION FOR	R SEQ ID NO:60:
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5	(i)	(A) (B) (C) (D)	LENG TYPE STRA	STH: E: nu ANDEL OLOGY CULE	2511 clei NESS	CTER bas c ac : si near	e pa id ngle	irs						
	( 3	(A) (B)	NAM LOC	ME/KE	ON: 1	odin 2 MATI	508	equer	ıce					
15	(3	ci) S	EQUE	ENCE	DESC	RIPT	: NOI	SEC	) ID	NO : 6	: 0			
20	 					GTG Val						Lys		48
25						CGC Arg							GAA Glu ,	96
	 			-		ATT Ile								144
30						AGT Ser 55								192
35	 					TGT Cys								240
40						GTG Val							_	288
45						AAG Lys								336
73						GCC Ala								384
50		Glu				CAG Gln 135							_	432
55						GAG Glu					Glu		GAA Glu 160	480

5							CGC Arg								528
5							ACT Thr 185								576
10							TGT Cys								624
15							TTG Leu								672
20							AAT Asn								720
25							CTG Leu					_	_		768
							ATC Ile 265								816
30							CCT Pro								864
35							TGC Cys								912
40	Asn				Asp		AAA Lys			Asn					960
45							GAC Asp		Gly					Ile	1008
				Leu				Val					Tyr	ATG Met	1056
50			val				Arg					Pro		TAC Tyr	1104
55		Let				туг					ı Gly			CCG Pro	1152

5									AAG Lys								1200
									TCC Ser								1248
10									ACG Thr 425								1296
15									GAG Glu								1344
20	Arg	Asn 450	Met	Asn	Phe	Lys	Arg 455	Leu	GAA Glu	Ala	Gly	Met 460	Leu	Asp	Pro	Pro	1392
25	Phe 465	Val	Pro	Asp	Pro	Arg 470	Ala	Val	TAC Tyr	Cys	Lys 475	Asp	Val	Leu	Asp	Ile 480	1440
	Glu	Gln	Phe	Ser	Thr 485	Val	Lys	Gly	GTC Val	Asn 490	Leu	Asp	His	Thr	Asp 495	Asp	1488
30	Asp	Phe	Tyr	Ser 500	Lys	Phe	Ser	Thr	GGC Gly 505	Ser	Val	Ser	Ile	Pro 510	Trp	Gln	1536
35	Asn	Glu	Met 515	Ile	Glu	Thr	Glu	Cys 520	TTT Phe	Lys	Glu	Leu	Asn 525	Val	Phe	Gly	1584
40									CTG Leu								1632
45									AGA Arg								1680
									TCC Ser								1728
50									AAC Asn 585								1776
55									AAG Lys								1824

e	-	GTG Val 610													1872
5		AGC Ser													1920
10		CTG Leu													1968
15		CTC Leu													2016
20		GAC Asp													2064
25		TAC Tyr 690													2112
		ACC Thr													2160
30		GAG Glu													2208
35		AAG Lys											Met		2256
40		AAG Lys						Val						AAC Asn	2304
45		GAG Glu 770					Leu							ACC Thr	2352
		Ile				Val					Asn			AGC Ser 800	2400
50					ser					Glu				ATG Met	2448
55				Phe					Gly				/ Met	GAC Asp	2496

131

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GAG CTG TAC AAG TAA
                                                                          2511
     Glu Leu Tyr Lys
             835
5
               (2) INFORMATION FOR SEQ ID NO:61:
           (i) SEQUENCE CHARACTERISTICS:
10
              (A) LENGTH: 836 amino acids
              (B) TYPE: amino acid
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
15
           (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
            (xi) SEQUENCE DESCRIPTION: SEO ID NO:61:
20
     Met Glu Leu Glu Asn Ile Val Ala Asn Thr Val Leu Leu Lys Ala Arg
     Glu Gly Gly Gly Lys Arg Lys Gly Lys Ser Lys Lys Trp Lys Glu
     Ile Leu Lys Phe Pro His Ile Ser Gln Cys Glu Asp Leu Arg Arg Thr
25
      Ile Asp Arg Asp Tyr Cys Ser Leu Cys Asp Lys Gln Pro Ile Gly Arg
                             55
     Leu Leu Phe Arg Gln Phe Cys Glu Thr Arg Pro Gly Leu Glu Cys Tyr
                         70
30
     Ile Gln Phe Leu Asp Ser Val Ala Glu Tyr Glu Val Thr Pro Asp Glu
                                          90
     Lys Leu Gly Glu Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro
                                      105
     Lys Ser Pro Val Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln
35
                                 120
     Thr Glu Glu Lys Leu Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala
                             135
     Cys Ala Gln Ser Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu
                         150
                                              155
40
     Tyr Leu Asp Ser Met Phe Phe Asp Arg Phe Leu Gln Trp Lys Trp Leu
                     165
                                         170
     Glu Arg Gln Pro Val Thr Lys Asn Thr Phe Arg Gln Tyr Arg Val Leu
                                     185
     Gly Lys Gly Gly Phe Gly Glu Val Cys Ala Cys Gln Val Arg Ala Thr
45
                                 200
     Gly Lys Met Tyr Ala Cys Lys Arg Leu Glu Lys Lys Arg Ile Lys Lys
                             215
     Arg Lys Gly Glu Ser Met Ala Leu Asn Glu Lys Gln Ile Leu Glu Lys
                                              235
50
     Val Asn Ser Gln Phe Val Val Asn Leu Ala Tyr Ala Tyr Glu Thr Lys
                     245
                                          250
     Asp Ala Leu Cys Leu Val Leu Thr Ile Met Asn Gly Gly Asp Leu Lys
                                      265
      Phe His Ile Tyr Asn Met Gly Asn Pro Gly Phe Glu Glu Glu Arg Ala
55
                                  280
```

131

Leu Phe Tyr Ala Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg

		290					295					300				
	Glu 305	Asn	Thr	Val	Tyr	Arg 310	Asp	Leu	Lys	Pro	Glu 315	Asn	Ile	Leu	Leu	Asp 320
5	Asp	Tyr	Gly	His	Ile 325	Arg	Ile	Ser	Asp	Leu 330	Gly	Leu	Ala	Val	Lys 335	Ile
	Pro	Glu	Gly	Asp 340	Leu	Ile	Arg	Gly	Arg 345	Val	Gly	Thr	Val	Gly 350	Tyr	Met
			Glu 355					360		_	_		365			
10	Trp	Gly 370	Leu	Gly	Cys	Leu	Ile 375	Tyr	Glu	Met	Ile	Glu 380	Gly	Gln	Ser	Pro
	385		Gly	_	-	390	-		_	_	395			_	_	400
15			Glu		405			_		410	_				415	
	_		Ile	420					425		_			430		
00	-	_	Gln 435			_		440			_		445			
20	_	450	Met			_	455				_	460				
	465		Pro			470					475					480
25			Phe		485		_	_		490		_			495	_
	-		Tyr Met	500	-				505					510	_	
30			515 Gly					520		-			525			
50		530	Lys				535	_				540				
	545		Ser	-	_	550					555					560
35			Ser	_	565					570					575	
			Val	580					585					590		
40			595 Pro					600	_				605			
40		610					615		-	_	_	620				
	625				_	630	_				635		-			Leu 640
45					645					650					655	
				660					665			_		670		Tyr
50		_	675		-			680			_		685			Glu
50	-	690				_	695				_	700				Tyr
	705		_			710	_			_	715	;				720
55				_	725		_		-	730	)				735	Gly Ala
	пlS	∵ bys	, nan	ں بی	. туг	W-Dil	· · · y I	. ASI	· oct		· wor	. val	. <u>-</u> γ1		. McL	

				740					745					750			
	Asp	Lys	Gln 755	Lys	Asn	Gly	Ile	Lys 760	Val	Asn	Phe	Lys	Ile 765	Arg	His	Asn	
5		770			Ser		775					780					
		Ile	Gly	Asp	Gly		Val	Leu	Leu	Pro		Asn	His	Tyr	Leu		
	785 Thr	Gln	Ser	Ala	Leu	790 Ser	Lys	Asp	Pro		795 Glu	Lys	Arg	Asp		800 Met	
10	Val	Leu	Leu	Glu 820	805 Phe	Val	Thr	Ala		810 Gly	Ile	Thr	Leu		815 Met	Asp	
	Glu	Leu	Tyr 835						825					830			
15			(2)	INI	FORM	MOITA	I FOR	R SE(	Q ID	NO:	52:						
		(1	(A)	LENG	NCE ( STH: E: nu	1893	bas	se pa									
20					ANDEI			_	9								
25				OLEC	CULE JRE :	TYPE	E: cI	ONA									
2.0			(B)	LOC	ME/KE CATION HER I	N: 1	L]	1890	equer	ıce							
30		()	ci) S	EQUE	ENCE	DESC	CRIPT	rion	: SE(	O ID	NO : 6	52:					
30		AGC	AGA	AGC	AAG	CGT	GAC	AAC	AAT	ттт	TAT	AGT					48
30		AGC	AGA	AGC		CGT	GAC	AAC	AAT	ттт	TAT	AGT					48
30 35	Met 1	AGC Ser	AGA Arg	AGC Ser	AAG Lys 5	CGT Arg	GAC Asp	AAC Asn	AAT Asn	TTT Phe 10	TAT Tyr	AGT Ser	Val	Glu	Ile 15	Gly	
	Met 1 GAT	AGC Ser	AGA Arg ACA	AGC Ser	AAG Lys	CGT Arg GTC	GAC Asp CTG	AAC Asn AAA	AAT Asn	TTT Phe 10	TAT Tyr CAG	AGT Ser	Val TTA	Glu AAA	Ile 15 CCT	Gly ATA	48 96
	Met 1 GAT Asp	AGC Ser TCT Ser	AGA Arg ACA Thr	AGC Ser TTC Phe 20	AAG Lys 5 ACA Thr	CGT Arg GTC Val	GAC Asp CTG Leu	AAC Asn AAA Lys GTA	AAT Asn CGA Arg 25	TTT Phe 10 TAT Tyr	TAT Tyr CAG Gln GCT	AGT Ser AAT Asn	Val TTA Leu GAT	Glu AAA Lys 30 GCC	Ile 15 CCT Pro	Gly ATA Ile CTT	
35	Met 1 GAT Asp	AGC Ser TCT Ser	AGA Arg ACA Thr	AGC Ser TTC Phe 20	AAG Lys 5 ACA Thr	CGT Arg GTC Val	GAC Asp CTG Leu	AAC Asn AAA Lys GTA	AAT Asn CGA Arg 25	TTT Phe 10 TAT Tyr	TAT Tyr CAG Gln GCT	AGT Ser AAT Asn	Val TTA Leu GAT	Glu AAA Lys 30 GCC	Ile 15 CCT Pro	Gly ATA Ile CTT	96
35 40	Met 1 GAT Asp GGC Gly	AGC Ser TCT Ser TCA Ser	AGA Arg ACA Thr GGA Gly 35	AGC Ser TTC Phe 20 GCT Ala	AAG Lys 5 ACA Thr CAA Gln	CGT Arg GTC Val GGA Gly	GAC Asp CTG Leu ATA Ile	AAC Asn AAA Lys GTA Val 40	AAT Asn CGA Arg 25 TGC Cys	TTT Phe 10 TAT Tyr GCA Ala	TAT Tyr CAG Gln GCT Ala	AGT Ser AAT Asn TAT Tyr	TTA Leu GAT Asp 45	AAA Lys 30 GCC Ala	Ile 15 CCT Pro ATT Ile	ATA Ile  CTT Leu  CAG	96
35	Met 1 GAT Asp GGC Gly	AGC Ser TCT Ser TCA Ser	AGA Arg ACA Thr GGA Gly 35	AGC Ser TTC Phe 20 GCT Ala	AAG Lys 5 ACA Thr CAA Gln	CGT Arg GTC Val GGA Gly	GAC Asp CTG Leu ATA Ile	AAC Asn AAA Lys GTA Val 40	AAT Asn CGA Arg 25 TGC Cys	TTT Phe 10 TAT Tyr GCA Ala	TAT Tyr CAG Gln GCT Ala	AGT Ser AAT Asn TAT Tyr	TTA Leu GAT Asp 45	AAA Lys 30 GCC Ala	Ile 15 CCT Pro ATT Ile	ATA Ile  CTT Leu  CAG	96 144
35 40	GAT Asp GGC Gly GAA Glu	AGC Ser TCT Ser TCA Ser AGA Arg 50 CAT	AGA Arg ACA Thr GGA Gly 35 AAT Asn	AGC Ser  TTC Phe 20  GCT Ala  GTT Val	AAG Lys 5 ACA Thr CAA Gln GCA Ala	CGT Arg GTC Val GGA Gly ATC Ile	GAC Asp CTG Leu ATA Ile AAG Lys 55	AAC ASN AAA Lys GTA Val 40 AAG Lys	AAT Asn CGA Arg 25 TGC Cys CTA Leu	TTT Phe 10 TAT Tyr GCA Ala AGC Ser	TAT Tyr CAG Gln GCT Ala CGA Arg	AGT Ser AAT Asn TAT Tyr CCA Pro 60 CTT	TTA Leu GAT Asp 45 TTT Phe	AAA Lys 30 GCC Ala CAG Gln	Ile 15 CCT Pro ATT Ile AAT Asn	ATA Ile  CTT Leu  CAG Gln  GTT	96 144
35 40	GAT Asp GGC Gly GAA Glu	AGC Ser TCT Ser TCA Ser AGA Arg 50 CAT	AGA Arg ACA Thr GGA Gly 35 AAT Asn	AGC Ser  TTC Phe 20  GCT Ala  GTT Val	AAG Lys 5 ACA Thr CAA Gln GCA Ala	CGT Arg GTC Val GGA Gly ATC Ile	GAC Asp CTG Leu ATA Ile AAG Lys 55	AAC ASN AAA Lys GTA Val 40 AAG Lys	AAT Asn CGA Arg 25 TGC Cys CTA Leu	TTT Phe 10 TAT Tyr GCA Ala AGC Ser	TAT Tyr CAG Gln GCT Ala CGA Arg	AGT Ser AAT Asn TAT Tyr CCA Pro 60 CTT	TTA Leu GAT Asp 45 TTT Phe	AAA Lys 30 GCC Ala CAG Gln	Ile 15 CCT Pro ATT Ile AAT Asn	ATA Ile  CTT Leu  CAG Gln  GTT	96 144 192
35 40 45	GAT Asp GGC Gly GAA Glu ACT Thr 65	AGC Ser TCT Ser TCA Ser AGA Arg 50 CAT His	AGA Arg ACA Thr GGA Gly 35 AAT Asn GCC Ala	AGC Ser TTC Phe 20 GCT Ala GTT Val AAG Lys	AAG Lys 5 ACA Thr CAA Gln GCA Ala CGG Arg	CGT Arg GTC Val GGA Gly ATC Ile GCC Ala 70	GAC Asp CTG Leu ATA Ile AAG Lys 55 TAC Tyr	AAC ASN AAA Lys GTA Val 40 AAG Lys AGA Arg	AAT Asn  CGA Arg 25  TGC Cys  CTA Leu  GAG Glu	TTT Phe 10 TAT Tyr GCA Ala AGC Ser CTA Leu	TAT Tyr CAG Gln GCT Ala CGA Arg GTT Val 75	AGT Ser AAT Asn TAT Tyr CCA Pro 60 CTT Leu	TTA Leu GAT Asp 45 TTT Phe ATG Met	AAA Lys 30 GCC Ala CAG Gln AAA Lys	Ile 15 CCT Pro ATT Ile AAT Asn TGT Cys	Gly ATA Ile CTT Leu CAG Gln GTT Val 80 AAA	96 144 192
35 40 45	GAT Asp GGC Gly GAA Glu ACT Thr 65	AGC Ser TCT Ser TCA Ser AGA Arg 50 CAT His	AGA Arg ACA Thr GGA Gly 35 AAT Asn GCC Ala	AGC Ser TTC Phe 20 GCT Ala GTT Val AAG Lys	AAG Lys 5 ACA Thr CAA Gln GCA Ala	CGT Arg GTC Val GGA Gly ATC Ile GCC Ala 70	GAC Asp CTG Leu ATA Ile AAG Lys 55 TAC Tyr	AAC ASN AAA Lys GTA Val 40 AAG Lys AGA Arg	AAT Asn  CGA Arg 25  TGC Cys  CTA Leu  GAG Glu	TTT Phe 10 TAT Tyr GCA Ala AGC Ser CTA Leu	TAT Tyr CAG Gln GCT Ala CGA Arg GTT Val 75	AGT Ser AAT Asn TAT Tyr CCA Pro 60 CTT Leu	TTA Leu GAT Asp 45 TTT Phe ATG Met	AAA Lys 30 GCC Ala CAG Gln AAA Lys	Ile 15 CCT Pro ATT Ile AAT Asn TGT Cys	Gly ATA Ile CTT Leu CAG Gln GTT Val 80 AAA	96 144 192 240

	Ser	Leu	Glu	Glu 100	Phe	Gln	Asp	Val	Tyr 105	Ile	Val	Met	Glu	Leu 110	Met	Asp	
5										GAG Glu							384
10										GGA Gly							432
15										CCC Pro							480
										TTC Phe 170							528
20										GTA Val							576
25										TAC Tyr						TTA Leu	624
30										ATG Met					_		672
35																CAG Gln 240	720
										AAG Lys 250							768
40															Phe	GAG Glu	816
45				Pro					Pro					His		AAA Lys	864
50								Asp					Met			ATA	912
55		Ala					Ser					Let				TAC Tyr 320	960
	ATC	AAT	GTC	TGG	TAT	GAT	CCT	TCI	GAA	GCA	GAA	GCI	CCA	CCF	CCF	AAG	1008

										135							
	Ile	Asn	Val	Trp	Tyr 325	Asp	Pro	Ser	Glu	Ala 330	Glu	Ala	Pro	Pro	Pro 335	Lys	
												ACA					1056
5	Ile	Pro	Asp	Lys 340	Gln	Leu	Asp	Glu	Arg 345	Glu	His	Thr	Ile	Glu 350	Glu	Trp	
												GAG					1104
10	Lys	Glu	Leu 355	Ile	Tyr	Lys	Glu	Val 360	Met	Asp	Leu	Glu	365	Arg	Thr	ràs	
												GCA					1152
45	Asn	370	vaı	116	Arg	GIY	375	PIO	ser	Pro	Leu	Ala 380	GIII	vai	GIII	GIII	
15	TGG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	1200
	Trp					Ala					Lys	Gly				Phe	
	385					390					395					400	
20												GGC					1248
	Thr	Gly	Val	Val	Pro 405	Ile	Leu	Val	Glu	Leu 410	Asp	Gly	Asp	Val	Asn 415	Gly	
25												GAT Asp				_	1296
23	nis	гуу	FIIE	420	vai	261	Gry	Giu	425	Giu	Gry	ASP	ALG	430	171	Cly	
		ama		ama	220	mma	n ma	maa	7.00	200	000	3 3 C	OTT C	aaa	CTPC	CCC	1344
												AAG Lys					1344
30	•		435		_			440			-		445				
	TGG	CCC	ACC	CTC	GTG	ACC	ACC	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	1392
												Val					
35		450					455					460					
00																ATG	1440
		Tyr	Pro	Asp	His	Met 470	Lys	Gln	His	qaA	Phe 475	Phe	Lys	Ser	Ala	Met 480	
	465					4/0					4/3					400	
40												TTC					1488
	Pro	GIu	GIY	Tyr	Val 485	GIN	GIU	Arg	unr	11e	Pne	Phe	ьуs	Asp	495		
45					-							GGC Gly				GTG Val	1536
40	ADII	171	Ly S	500			O.L.	, , ,	505		014	. 017	ш	510			
	330	aca	אתיים	C N C	CTP.C	7 7 C	CCC	አጥሮ	CAC	mma	י אאר	- CAC	GNC	ccc	י אארי	ATC	1584
																Ile	1304
50		_	515			_		520					525				
	СТС	GGG	CAC	AAG	CTG	GAG	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	1632
							Tyr	Asn				His	Asn			Ile	
55		530					535					540					•
55	ATG	GCC	GAC	AAG	CAG	AAG	AAC	GGC	ATC	: AAG	GTO	AAC	TTC	AAC	ATC	CGC	1680

									•	136							
	Met . 545	Ala	Asp	Lys		Lys 550	Asn	Gly	Ile	Lys	Val 555	Asn	Phe	Lys	Ile	Arg 560	
5	CAC																1728
10	AAC Asn																1776
15					TCC Ser												1824
13					CTG Leu												1872
20					TAC Tyr		TAA										1893
25		<b>(</b> )	, ,		FORM!				-	NO:	63:						
30		·	(B)	TYP STR	ETH: E: an ANDEI OLOG	nino ONES	acio S: s	d ingl									
35		(-	ν) F	RAGM	ENCE	TYPE	: in	tern	al	Q ID	NO:	63:					
	1				5					10					15	Gly	
40				20					25					30		o Ile e Leu	
			35					40					45			n Gln	
45	Thr 65	50 His	Ala	Lys	Arg	Ala	55 Tyr	Arg	g Glu	ı Lev	val 75	60 L Leu	ı Met	. Ly	s Су	s Val 80	
	Asn		_		85	Ile				90	ı Val				95	n Lys	
50				100	)				109	5				11	0	t Asp	
			115	5				120	)				125	5		g Met s Ser	
55		130	)				139	5				14	0			l Lys	

	145					150					155					160
	Ser	Asp	Cys	Thr	Leu 165	Lys	Ile	Leu	Asp	Phe 170	Gly	Leu	Ala	Arg	Thr 175	Ala
5	Gly	Thr	Ser	Phe 180	Met	Met	Thr	Pro	Tyr 185	Val	Val	Thr	Arg	Tyr 190	Tyr	Arg
			Glu 195					200		_	_		205		_	
		210	Val				215					220				
10	225		Gly			230					235					240
			Thr		245					250	_				255	
15			Tyr	260					265	_		-	-	270		
			Phe 275					280			_		285			_
		290	Ala				295					300				
20	305		Ser			310					315					320
			Val		325					330					335	_
25			Asp	340					345					350		
			155 355					360					365			
00		370	Val				375					380				
30	385		Pro			390					395	_				400
			Val		405					410					415	
35			Phe	420					425		_	_		430	_	_
			Thr 435					440			-	-	445			
40		450	Thr				455			_	_	460		_		
40	465		Pro			470	_			_	475		-			480
			Gly		485					490			-		495	_
45			Lys	500					505			_	_	510		
			Ile 515					520					525			
50		530	His				535					540			_	
50	545		Asp			550					555					560
			Ile		565					570				-	575	
55			Pro	580					585					590		
	Leu	ser	Thr	Gln	ser	Ala	Leu	Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp

	His N	Met '				$\epsilon$	_	00 /al T	Chr A	la A			05 [le T	hr L	eu (	Ξlγ		
5	625	F			_	530												
			(2)	INF	ORMA!	rion	FOR	SEQ	ID N	10 : 64	:							
		(i	) SE	QUEN	CE C	HARAG	CTER	ISTIC	CS:									
10			(A) : (B) : (C) : (D) :	TYPE STRA	: nu	cleio NESS	c ac:	id	irs									
15			.i) M .x) F			TYPE	: cD	NA										
20			(B) (D)	LOC	E/KE ATIO ER I	N: 1 NFOR	1 MATI	818 ON:										
		(>	ci) S	EQUE	NCE	DESC	RIPT	: NOI	SEQ	ID :	ио : 6	4:						
25			CAG Gln						Tyr								48	
30	ATC Ile	TGG Trp	GAG Glu	GTG Val 20	CCC Pro	GAG Glu	CGT Arg	TAC Tyr	CAG Gln 25	AAC Asn	CTG Leu	TCT Ser	CCA Pro	GTG Val 30	GGC Gly	TCT Ser	96	
0.5	GGC Gly	GCC Ala	TAT Tyr 35	GGC Gly	TCT Ser	GTG Val	TGT Cys	GCT Ala 40	GCT Ala	TTT Phe	GAC Asp	ACA Thr	AAA Lys 45	ACG Thr	GGG Gly	TTA Leu	144	
35	CGT Arg	GTG Val 50	GCA Ala	GTG Val	AAG Lys	AAG Lys	CTC Leu 55	TCC Ser	AGA Arg	CCA Pro	TTT Phe	CAG Gln 60	TCC Ser	ATC Ile	ATT Ile	CAT His	192	
40	GCG Ala 65	AAA Lys	AGA Arg	ACC Thr	TAC Tyr	AGA Arg 70	GAA Glu	CTG Leu	CGG Arg	TTA Leu	CTT Leu 75	AAA Lys	CAT His	ATG Met	TA3	CAT His 80	240	
45	GAA Glu	TAA naA	GTG Val	ATT Ile	GGT Gly 85	CTG Leu	TTG Leu	GAC Asp	GTT Val	TTT Phe 90	ACA Thr	CCT Pro	GCA Ala	AGG Arg	TCT Ser 95	CTG Leu	288	
50					Asp										Ala	GAT Asp	336	
	CTG Lev	AAC Asr	AAC Asn 115	ılle	GTG Val	AAA Lys	TGT Cys	CAG Gln 120	Lys	CTT Leu	ACA Thr	GAT Asp	GAC Asp 125	His	GTI Val	CAG LGln	384	
55	TTC	CT	TA T	TAC	CAA	ATT	CTC	CGP	GGI	CTA	AAG	TAT	T ATA	CAT	TC	A GCT	432	138

									1	.00								
	Phe	Leu 130	Ile	Tyr	Gln	Ile	Leu 135	Arg	Gly	Leu	Lys	Tyr 140	Ile	His	Ser	Ala		
5														GTG Val			480	
10														CAC His			528	
45	GAT Asp	GAA Glu	ATG Met	ACA Thr 180	GGC Gly	TAC Tyr	GTG Val	GCC Ala	ACT Thr 185	AGG Arg	TGG Trp	TAC Tyr	AGG Arg	GCT Ala 190	CCT Pro	GAG Glu	576	
15	ATC Ile	ATG Met	CTG Leu 195	AAC Asn	TGG Trp	ATG Met	CAT His	TAC Tyr 200	AAC Asn	CAG Gln	ACA Thr	GTT Val	GAT Asp 205	ATT Ile	TGG Trp	TCA Ser	624	
20	GTG Val	GGA Gly 210	TGC Cys	ATA Ile	ATG Met	GCC Ala	GAG Glu 215	CTG Leu	TTG Leu	ACT Thr	GGA Gly	AGA Arg 220	ACA Thr	TTG Leu	TTT Phe	CCT Pro	672	
25	GGT Gly 225	Thr	GAC Asp	CAT His	ATT Ile	GAT Asp 230	CAG Gln	TTG Leu	AAG Lys	CTC Leu	ATT Ile 235	TTA Leu	AGA Arg	CTC Leu	GTT Val	GGA Gly 240	720	
30														TCT Ser		Arg	768	
25	AAC Asn	TAT	ATT	CAG Gln 260	Ser	TTG Leu	ACT Thr	CAG Gln	ATG Met 265	Pro	AAG Lys	ATG Met	AAC Asn	TTT Phe 270	GCG Ala	AAT Asn	816	
35				Gly					Ala					Glu		ATG Met	864	
40	CTT Leu	GTA Val	Leu	GAC Asp	TCA Ser	GAT Asp	AAG Lys 295	Arg	ATT	ACA Thr	GCG Ala	GCC Ala 300	Gln	GCC Ala	CTI Lev	GCA Ala	912	
45		Ala					туг					Asp				G GCC L Ala 320	960	
50						ı Sei					g Asp					r GAG o Glu 5	1008	
	TG( Tr <sub>I</sub>	AA D Ly:	A AGO	C CTO	ı Thi	TA:	r GA:	GAZ Glu	A GT( 1 Va: 34!	l Ile	C AGO	C TT	r GT( e Vai	3 CC <i>I</i> 1 Pro 350	o Pr	A CCC o Pro	1056	
55	CT	r ga	C CAI	A GA	A GAG	TA E	G GA	G TC	C GA	g gar	r cci	A CC	G GT	C GC	C AC	C ATG	1104	139

										70							
	Leu	Asp	Gln 355	Glu	Glu	Met	Glu	Ser 360	Glu	ĄsĄ	Pro	Pro	Val 365	Ala	Thr	Met	
5									ACC Thr								1152
10									CAC His								1200
45									AAG Lys								1248
15									TGG Trp 425								1296
20									CGC Arg								1344
25									CCC Pro								1392
30		Ile							AAC Asn								1440
25									AAC Asn							Ile	1488
35					Asp										Tyr	AAC Asn	1536
40				His					Met					Lys		: GGC . Gly	1584
45			Val					Arg					ı Asp			GTG Val	1632
50		ı Lev					Glr					Ile				C CCC y Pro 560	1680
r-						Asr					Thi					G AGC 1 Ser 5	1728
55	AA	A GAC	2 220	C AAC	C GAG	AAC	G CGC	C GA	r cac	TA C	G GT	C CTC	G CT	G GAG	3 TT	C GTG	1776

141

Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 580 585 ACC GCC GCG GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA 1821 5 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys (2) INFORMATION FOR SEQ ID NO:65: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 606 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single 15 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65: Met Ser Gln Glu Arg Pro Thr Phe Tyr Arg Gln Glu Leu Asn Lys Thr Ile Trp Glu Val Pro Glu Arg Tyr Gln Asn Leu Ser Pro Val Gly Ser 25 25 Gly Ala Tyr Gly Ser Val Cys Ala Ala Phe Asp Thr Lys Thr Gly Leu 40 Arg Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Ser Ile Ile His 55 30 Ala Lys Arg Thr Tyr Arg Glu Leu Arg Leu Leu Lys His Met Lys His Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Arg Ser Leu 90 Glu Glu Phe Asn Asp Val Tyr Leu Val Thr His Leu Met Gly Ala Asp 35 105 Leu Asn Asn Ile Val Lys Cys Gln Lys Leu Thr Asp Asp His Val Gln 120 125 Phe Leu Ile Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala 135 40 Asp Ile Ile His Arg Asp Leu Lys Pro Ser Asn Leu Ala Val Asn Glu 150 155 Asp Cys Glu Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg His Thr Asp 165 170 Asp Glu Met Thr Gly Tyr Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu 45 185 Ile Met Leu Asn Trp Met His Tyr Asn Gln Thr Val Asp Ile Trp Ser 200 Val Gly Cys Ile Met Ala Glu Leu Leu Thr Gly Arg Thr Leu Phe Pro 215 220 50 Gly Thr Asp His Ile Asp Gln Leu Lys Leu Ile Leu Arg Leu Val Gly 230 235 Thr Pro Gly Ala Glu Leu Leu Lys Lys Ile Ser Ser Glu Ser Ala Arg 245 250 Asn Tyr Ile Gln Ser Leu Thr Gln Met Pro Lys Met Asn Phe Ala Asn 55 265 Val Phe Ile Gly Ala Asn Pro Leu Ala Val Asp Leu Leu Glu Lys Met

PCT/DK98/00145 WO 98/45704

142

			275					280					285			
	Leu	Val 290	Leu	Asp	Ser	Asp	Lys 295		Ile	Thr	Ala	Ala 300		Ala	Leu	Ala
5	His 305	Ala	Tyr	Phe	Ala	Gln 310	Tyr	His	Asp	Pro	Asp 315	Asp	Glu	Pro	Val	Ala 320
Ü		Pro	Tyr	Asp	Gln 325		Phe	Glu	Ser	Arg 330		Leu	Leu	Ile	Asp 335	
	Trp	Lys	Ser			Tyr	qaA	Glu			Ser	Phe	Val	Pro		Pro
10	Leu	Asp	Gln	340 Glu	Glu	Met	Glu		345 Glu	Asp	Pro	Pro			Thr	Met
	Val		355 Lys	Gly	Glu	Glu		360 Phe	Thr	Gly	Val		365 Pro	Ile	Leu	Val
45		370 Leu	Asp	Gly	Asp		375 Asn	Gly	His	Lys		380 Ser	Val	Ser	Gly	
15	385 Gly	Glu	Gly	Asp		390 Thr	Tyr	Gly	Lys		395 Thr	Leu	Lys	Phe		400 Cys
	Thr	Thr	Gly		405 Leu	Pro	Val	Pro		410 Pro	Thr	Leu	Val		415 Thr	Leu
20	Thr	Туr	Gly	420 Val	Gln	Cys	Phe	Ser	425 Arg	Tyr	Pro	Asp	His	430 Met	Lys	Gln
	His	Asp	435 Phe	Phe	Lys	Ser	Ala	440 Met	Pro	Glu	Gly	Tyr	445 Val	Gln	Glu	Arg
	Thr	450 Ile	Phe	Phe	Lys	Asp	455 Asp	Gly	Asn	Tyr	Lys	460 Thr	Arg	Ala	Glu	۷al
25	465	nh -	<b>~1</b>	G2	7	470	T	3703	7	7	475	<b>01.</b> .	T 0	T	Clyr	480
	-		Glu	_	485					490					495	
	_		Lys	500					505					510		
30	•		Ser 515				_	520				_	525			
		530	Val				535					540				
35	Gln 545	Leu	Ala	Asp	His	Tyr 550	Gln	Gln	Asn	Thr	Pro 555		Gly	Asp	Gly	Pro 560
	Val	Leu	Leu	Pro	Asp 565		His	Tyr	Leu	Ser 570	Thr	Gln	Ser	Ala	Leu 575	
	Lys	Asp	Pro	Asn 580	Glu	Lys	Arg	Asp	His 585		Val	Leu	Leu	Glu 590	Phe	Val
40	Thr	Ala	Ala 595	Gly	Ile	Thr	Leu	Gly 600		Asp	Glu	Leu	Tyr 605			
			(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	66:					
45		,	: )	FOITE	MOTE	CITA D	n come	n T Cm	TOO.							
40		`		LEN TYP	GTH:	291	3 ba	se p								
			(C)	STR	ANDE	DNES	S: s	ingl	e							
50				TOP												
			ii) ix)				E: c	:DNA								
55			(B	AN (.	CATI	ON:	1	2910	)	nce						

142

(D) OTHER INFORMATION:

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

5		AGT Ser															48
10		AGA Arg													_	_	96
15		AAA Lys															144
.0		CCT Pro 50													_	_	192
20		AGG Arg															240
25		ATC Ile															288
30		GCA Ala													_	_	336
35		ACT Thr															384
		CCT Pro 130															432
40		TGT Cys					Arg					Ser					480
45		CGA Arg									Ser					Met	528
50		GAT Asp			Val					Phe					Leu		576
55		CCA Pro		Pro					Ala					Met	_		624
	TTA	. GCT	CCA	GAA	. GTA	CAA	AGC	TCC	GAA	GAA	TAT	TTA	CAG	CTA	TTG	AAG	672

	Leu	Ala 210	Pro	Glu	Val	Gln	Ser 215	Ser	Glu	Glu	Tyr	11e 220	Gln	Leu	Leu	Lys	
5					Ser					CAT His							720
10										CTC Leu 250							768
										GAA Glu							816
15										AAT Asn							864
20										TGG Trp							912
25										CCT Pro							960
30										AAT Asn 330							1008
										AAA Lys							1056
35				Leu					Ser	ACT Thr				Gly			1104
40			Thr					Gly		' AAC Asn			Ile				1152
45		Arg					Gly					Let				TCT Ser 400	1200
50						Ası					ı Glı					TAT Tyr	1248
					ı Asp					туз					з Ту	C CAA	1296
55	CAG	G GAT	CA!	A GT	r GT	C AA	A GAI	A GA	r aa'	r att	r ga	A GC	r gti	A GGG	G AA	AAA A	1344

										145							
	Gln	Asp	Gln 435	Val	Val	Lys	Glu	Asp 440	Asn	Ile	Glu	Ala	Val 445	Gly	Lys	Lys	
5				TAT Tyr													1392
10				GAA Glu													1440
45				ATT Ile													1488
15				ACC Thr 500													1536
20				GGC Gly													1584
25				AAG Lys													1632
30				GAC Asp													1680
25				AAC Asn												_	1728
35				TAC Tyr 580													1776
40				GAG Glu													1824
45			Glu	GAT Asp									Glu				1872
50		Val		AGC Ser								Asn					1920
E E				GGC Gly		Phe					Ser					Cys	1968
55	TAT	GCC	TGC	TCT	GTA	GTG	GTG	GAC	GGC	GAA	GTA	AAG	CAT	TG1	GTC	ATA	2016

										146							
	Tyr	Ala	Cys	Ser 660	Val	Val	Val	Asp	Gly 665	Glu	Val	ГÀЗ	His	Суs 670	Val	Ile	
5					ACT Thr												2064
10					GAA Glu												2112
15					TCC Ser												2160
, •					CAG Gln 725												2208
20					ACC Thr		-										2256
25					CAC His												2304
30					AAG Lys										_		2352
35					TGG Trp												2400
33					CGC Arg 805											Phe	2448
40					CCC Pro												2496
45				Gly					Arg					Phe		GGC	2544
50			Leu					Glu					Asp			GAG Glu	2592
55							His					Asn				CAC His 880	2640
	AAC	GTC	TAT	' ATC	ATG	GCC	GAC	' AAG	CAG	AAG	AAC	GGC	: ATC	AAG	GTG	AAC	2688

										147		•					
	Asn	Val	Tyr	Ile	Met 885	Ala	Asp	Lys	Gln	Lys 890	Asn	Gly	Ile	Lys	Val 895	Asn	
5											AGC Ser						2736
10											GGC Gly						2784
15											CTG Leu						2832
											TTC Phe 955						2880
20						GAC Asp					TAA						2913
25			(2)	INI	FORM	OITA	v FOI	R SE(	Q ID	NO:	57:						
30			(A) (B) (C) (D)	LENG TYPI STRA TOPO	STH: E: an ANDEI OLOGY	970 mino ONESS	amin acio S: s: inean	no ad ingle	cids e								
35		(7	/) FI	RAGMI	ent :	TYPI : TYPE : DES	int	cerna	al	Q ID	NO:	67:					
	Met 1	Ser	Ala	Glu	Gly 5	Tyr	Gln	Tyr	Arg	Ala 10	Leu	Tyr	Asp	Tyr	Lys 15	Lys	
40				20					25		Gly			30			
			35					40			Ser Tyr		45				
45		50					55				Glu	60					
	65 Lys	Ile	Ser	Pro		70 Thr	Pro	Lys	Pro	Arg	75 Pro	Pro	Arg	Pro	Leu	80 Pro	
50	Val	Ala	Pro		85 Ser	Ser	Lys	Thr		90 Ala	Asp	Val	Glu		95 Gln	Ala	
	Leu	Thr	Leu 115	100 Pro	Asp	Leu	Ala	Glu 120	105 Gln	Phe	Ala	Pro	Pro 125	110 Asp	Ile	Ala	
55	Pro	Pro 130	-	Leu	Ile	Lys	Leu 135		Glu	Ala	Ile	Glu 140		Lys	Gly	Leu	
	Glu	Cys	Ser	Thr	Leu	Tyr	Arg	Thr	Gln	Ser	Ser	Ser	Asn	Leu	Ala	Glu	

	145					150					155					160
	Leu	Arg	Gln	Leu	Leu 165	Asp	Cys	Asp	Thr	Pro 170	Ser	Val	Asp	Leu	Glu 175	Met
5		-		180				_	185		_		Tyr	190		
			195					200			-		Glu 205			
	Leu	Ala 210	Pro	Glu	Val	Gln	Ser 215	Ser	Glu	Glu	Tyr	Ile 220	Gln	Leu	Leu	Lys
10	Lys 225	Leu	Ile	Arg	Ser	Pro 230	Ser	Ile	Pro	His	Gln 235	Tyr	Trp	Leu	Thr	Leu 240
		_			245				-	250			Thr		255	
15				260					265				Ser	270		
			275					280					Asn 285			
		290					295			_		300	Arg			
20	305					310			_		315		Val			320
					325					330			Trp		335	
25	_			340					345	_			Asp	350		
	_		355			_	_	360			_		His 365			
		370					375	_				380	Ile			
30	385					390					395		Thr			400
					405					410			Leu		415	
35				420					425				Ser	430		
			435					440					Val 445			
		450		_			455				_	460	Arg			
40	465		_			470					475		Ile			480
					485					490			Ile		495	
45		•		500					505				Ile	510		
	Lys	Arg	Glu 515		Asn	Glu	Lys	Glu 520		Gln	Arg	Ile	Met 525		Asn	Туг
		530	ı				535					540				
50	Leu 545		Glu	Asp	Leu	Lys 550		Gln	Ala	Ala	Glu 555		Arg	Glu	Ile	Asp 560
	Lys	Arg	Met	Asn	Ser 565		Lys	Pro	qaA o	Leu 570		Gln	Leu	Arg	Lys 575	
55	_	_		580	)		_		585	;			Val	590	ł	
	Lvc	T.e.r	Δen	ദിം	יייייייייייייייייייייייייייייייייייייי	Len	G13/	her	(C) 1	Acr	ጥኩነ	· Gli	AST	· Glr	ጥላታን	- Sei

149

			595					600					605			
	Leu	Val 610	Glu	Asp	Asp	Glu	Asp 615	Leu	Pro	His	His	Asp 620		Lys	Thr	Trp
5	Asn 625	Val	Gly	Ser	Ser	Asn 630	Arg	Asn	Lys	Ala	Glu 635	Asn	Leu	Leu	Arg	Gly 640
	Lys	Arg	Asp	Gly	Thr 645	Phe	Leu	Val	Arg	Glu 650	Ser	Ser	Lys	Gln	Gly 655	Cys
	Tyr	Ala	Cys	Ser 660	Val	Val	Val	Asp	Gly 665	Glu	Val	Lys	His	Cys 670	Val	Ile
10	Asn	Lys	Thr 675	Ala	Thr	Gly	Tyr	Gly 680	Phe	Ala	Glu	Pro	Tyr 685	Asn	Leu	Tyr
	Ser	Ser 690	Leu	Lys	Glu	Leu	Val 695	Leu	His	Tyr	Gln	His 700	Thr	Ser	Leu	Val
15	Gln 705	His	Asn	Asp	Ser	Leu 710	Asn	Val	Thr	Leu	Ala 715	Tyr	Pro	Val	Tyr	Ala 720
	Gln	Gln	Arg	Arg	Gln 725	Asp	Pro	Pro	Val	Ala 730	Thr	Met	Val	Ser	Lys 735	Gly
	Glu	Glu	Leu	Phe 740	Thr	Gly	Val	Val	Pro 745	Ile	Leu	Val	Glu	Leu 750	Asp	Gly
20	Asp	Val	Asn 755	Gly	His	Lys	Phe	Ser 760	Val	Ser	Gly	Glu	Gly 765	Glu	Gly	Asp
	Ala	Thr 770	Tyr	Gly	Lys	Leu	Thr 775	Leu	Lys	Phe	Ile	Cys 780	Thr	Thr	Gly	Lys
25	Leu 785	Pro	Val	Pro	Trp	Pro 790	Thr	Leu	Val	Thr	Thr 795	Leu	Thr	Tyr	Gly	Val 800
	Gln	Cys	Phe	Ser	Arg 805	Tyr	Pro	Asp	His	Met 810	Lys	Gln	His	Asp	Phe 815	Phe
	Lys	Ser	Ala	Met 820	Pro	Glu	Gly	Tyr	Val 825	Gln	Glu	Arg	Thr	Ile 830	Phe	Phe
30	Lys	Asp	Asp 835	Gly	Asn	Tyr	Lys	Thr 840	Arg	Ala	Glu	Val	Lys 845	Phe	Glu	Gly
		Thr 850					855					860				
35	Asp 865	Gly	Asn	Ile	Leu	Gly 870	His	Lys	Leu	Glu	Tyr 875	Asn	Tyr	Asn	Ser	His 880
		Val			885					890		_			895	
		Lys		900					905					910		
40		Tyr	915					920					925			
		930					935					940				Asn
45	Glu 945	Lys	Arg	Asp	His	Met 950	Val	Leu	Leu	Glu	Phe 955	Val	Thr	Ala	Ala	Gly 960
40		Thr	Leu	Gly	Met 965		Glu	Leu	туг	Lys 970	933					960
50			(2)	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	68:					
- •		(:	i) SI	EQUE	NCE (	CHAR	ACTE	RIST	ICS:							
				LEN				-	airs							
				TYP					<b>-</b>							
			/				- · ·	9 -'	-							

149

(D) TOPOLOGY: linear

150

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

5

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...1785

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

	(x	i) S	EQUE	NCE	DESC	RIPT	'ION:	SEÇ	) ID	NO:6	8:					
10								AAG Lys								48
15								GAA Glu 25								96
20								TTG Leu						_		144
25								CGA Arg								192
20								AAG Lys								240
30								ACT Thr								288
35								GTC Val 105								336
40								ATG Met					Gly			384
45		Ser					Ile	GGA Gly				Glu			GCC Ala	432
40	Phe					Ile					Glu			_	Ser 160	480
50					Arg					Glu					GAC Asp	528
55				Ile					Phe					Arc	GTG Val	576

5													TAC Tyr 205				624
													GAC Asp				672
10													CCA Pro				720
15													TCT Ser				768
20	Arg	Phe	Pro	Ser 260	His	Phe	Ser	Ser	Asp 265	Leu	Lys	Asp	CTG Leu	Leu 270	Arg	Asn	816
25	Leu	Leu	Gln 275	Val	Asp	Leu	Thr	Lys 280	Arg	Phe	Gly	Asn	CTC Leu 285	Lys	Asp	Gly	864
	Val	Asn 290	Asp	Ile	Lys	Asn	His 295	Lys	Trp	Phe	Ala	Thr 300	ACT Thr	Asp	Trp	Ile	912
30											Phe 315		CCA Pro	Lys		Lys 320	960
35	Gly	Pro	Gly	qzA	Thr 325	Ser	Asn	Phe	Asp	Asp 330	Tyr	Glu	GAG Glu	Glu	Glu 335	Ile	1008
35	Gly CGG Arg	Pro GTC Val	Gly TCC Ser	ATC Ile 340	Thr 325 AAT Asn	Ser GAG Glu	Asn AAG Lys	Phe TGT Cys	Asp GGC Gly 345	Asp 330 AAG Lys	Tyr GAG Glu	Glu TTT Phe	Glu ACT Thr	Glu GAG Glu 350	Glu 335 TTT Phe	Ile GGG Gly	1008
	CGC	Pro GTC Val	TCC Ser	ASP ATC Ile 340 AGT	Thr 325 AAT Asn	Ser GAG Glu GGA	Asn AAG Lys GAA	TGT Cys	Asp GGC Gly 345 CTT	Asp 330 AAG Lys	Tyr GAG Glu ACT	Glu TTT Phe	Glu ACT	Glu GAG Glu 350 GTC	Glu 335 TTT Phe	Ile GGG Gly	
40	CGC Arg	Pro GTC Val GCC Ala	TCC Ser ATG Met 355	ASP ATC ile 340 AGT Ser	Thr 325 AAT Asn AAA Lys	GAG Glu GGA Gly	Asn AAG Lys GAA Glu	TGT Cys GAA Glu 360 GTT	Asp GGC Gly 345 CTT Leu	Asp 330 AAG Lys TTC Phe	GAG Glu ACT Thr	Glu TTT Phe GGA Gly	Glu ACT Thr GTT Val	GAG Glu 350 GTC Val	Glu 335 TTT Phe CCA Pro	GGG Gly ATT Ile	1056
40	CGC Arg CTT Leu GGA	GTC Val GCC Ala GTT Val 370 GAG	TCC Ser ATG Met 355 GAA Glu	ASP ATC Ile 340 AGT Ser TTA Leu GAA	Thr 325 AAT Asn AAA Lys GAT Asp	GAG Glu  GGA Gly  GGC Gly  GAT	ASN AAG Lys GAA Glu GAT ASP 375 GCA	TGT Cys GAA Glu 360 GTT Val	GGC Gly 345 CTT Leu AAT Asn	Asp 330 AAG Lys TTC Phe GGG Gly	GAG Glu ACT Thr CAA Gln	TTT Phe GGA Gly AAA Lys 380	Glu ACT Thr GTT Val 365	GAG Glu 350 GTC Val TCT Ser	Glu 335 TTT Phe CCA Pro GTT Val	GGG Gly ATT lle AGT Ser	1056

_	 CTC Leu	 										1296
5	CAG Gln											1344
10	AGA Arg 450											1392
15	GTC Val											1440
20	ATT Ile											1488
25	AAT Asn											1536
	GGC Gly										GGA Gly	1584
30									Pro		GAT Asp	1632
35	Pro							Ser			GCC Ala 560	1680
40							His				GAG Glu	1728
45			Ala			Gly				Туг	AAA Lys	1776
	CAG Gln											1788
50			IFORM				:69:				·	
EE	,		ENCE IGTH :									

152

(B) TYPE: amino acid(C) STRANDEDNESS: single

153

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

	Na - 1-	<b>~</b> 1	•		- 1			_	_		_				_	
	1				5					10				Glu	15	
10	Lys	Glu	Phe	Leu 20	Ala	Lys	Ala	Lys	Glu 25	ĄsĄ	Phe	Leu	Lys	Lys 30	Trp	Glu
	Asp	Pro	Ser 35	Gln	Asn	Thr	Ala	Gln 40	Leu	Asp	Gln	Phe	Asp 45	Arg	Ile	Lys
15	Thr	Leu 50	Gly	Thr	Gly	Ser	Phe 55	Gly	Arg	Val	Met	Leu 60	Val	Lys	His	Lys
	Glu 65	Ser	Gly	Asn	His	Tyr 70	Ala	Met	Lys	Ile	Leu 75	Asp	Lys	Gln	Lys	Val 80
	Val	Lys	Leu	Lys	Gln 85	Ile	Glu	His	Thr	Leu 90	Asn	Glu	Lys	Arg	Ile 95	
20	Gln	Ala	Val	Asn 100	Phe	Pro	Phe	Leu	Val 105		Leu	Glu	Phe	Ser 110	-	Lys
	Asp	Asn	Ser 115		Leu	Tyr	Met	Val 120		Glu	Tyr	Val	Ala 125	Gly	Gly	Glu
25	Met	Phe 130		His	Leu	Arg	Arg		Gly	Arg	Phe	Ser 140		Pro	His	Ala
	Arg 145		Tyr	Ala	Ala	Gln 150		Val	Leu	Thr	Phe		Tyr	Leu	His	Ser 160
		Asp	Leu	Ile	Tyr 165		Asp	Leu	Lys	Pro 170		Asn	Leu	Leu		
30	Gln	Gln	Gly	Tyr 180		Gln	Val	Thr	Asp		Gly	Phe	Ala	Lys	175 Arg	Val
	Lys	Gly	Arg		Trp	Thr	Leu			Thr	Pro	Glu		190 Leu	Ala	Pro
35	Glu			Leu	Ser	Lys		200 Tyr	Asn	Lys	Ala		205 Asp	Trp	Trp	Ala
33		210 Gly	Val	Leu	Ile		215 Glu	Met	Ala	Ala		220 Tyr	Pro	Pro	Phe	
	225 Ala	Asp	Gln	Pro		230 Gln	Ile	Tyr	Glu		235 Ile	Val	Ser	Gly		240 Val
40	Arg	Phe	Pro		245 His	Phe	Ser	Ser		250 Leu	Lys	Asp	Leu	Leu	255 Arg	Asn
	Leu	Leu		260 Val	Asp	Leu	Thr		265 Arg	Phe	Gly	Asn		270 Lys	Asp	Gly
45	Val		275 Asp	Ile	Lys	Asn		280 Lys	Trp	Phe	Ala		285 Thr	Asp	Trp	Ile
45		290 Ile	Tyr	Gln	Arg		295 Val	Glu	Ala	Pro		300 Ile	Pro	Lys	Phe	Lys
	305 Gly	Pro	Gly	Asp		310 Ser	Asn	Phe	Asp		315 Tyr	Glu	Glu	Glu	Glu	320 Ile
50	Arg	Val	Ser	Ile	325 Asn	Glu	Lys	Cys	Gly	330 Lys	Glu	Phe	Thr	Glu	335 Phe	Gly
	Arg	Ala	Met	340 Ser	Lys	Gly	Glu	Glu	345 Leu	Phe	Thr	Gly	Val	350 Val	Pro	Ile
			355					360					365	Ser		
55		370					375					380		Leu		
	_				_	- 2			- 1 -	1	1				-, -	

PCT/DK98/00145

	385					390					395					400	
	Ile	Cys	Thr	Thr	Gly 405	Lys	Leu	Pro	Val	Pro 410	Trp	Pro	Thr	Leu	Val 415	Thr	
5	Thr	Leu	Thr	Tyr 420	Gly	Val	Gln	Cys	Phe 425	Ser	Arg	Tyr	Pro	Asp 430	His	Met	
J	Lys	Gln	His 435		Phe	Phe	Lys	Ser 440		Met	Pro	Glu	Gly 445		Val	Gln	
	Glu			Ile	Phe	Tyr	Lys 455		Asp	Gly	Asn	Tyr 460		Thr	Arg	Ala	
10		450 Val	Lys	Phe	Glu			Thr	Leu	Val			Ile	Glu	Leu	Lys 480	
	465	_			_	470	_		_		475	~7	***	Y	Mak		
	-		_		485					Ile 490					495		
15	Tyr	Asn	Tyr	Asn 500	Ser	His	Asn	Val	Tyr 505	Ile	Met	Ala	Asp	Lys 510	Pro	Lys	
10	Asn	Gly	Ile 515		Val	Asn	Phe	Lys 520		Arg	His	Asn	Ile 525	Lys	Asp	Gly	
	Ser	Val		Leu	Ala	Asp			Gln	Gln	Asn		Pro	Ile	Gly	Asp	
		530					535					540			_	- 2	
20	-	Pro	Val	Leu	Leu	Pro 550	Asp	Asn	His	Tyr	Leu 555		Thr	Gln	Ser	Ala 560	
	545 Leu	Ser	Lvs	Asp	Pro		Glu	Lys	Arg	Asp			Ile	Leu	Leu	Glu	
					565					570					575		
	Phe	Val	Thr		Ala	Gly	Ile	Thr			Met	Asp	Glu			Lys	
25	Pro	Gln	Glu	580					585					590			
			595														
			(2	) IN	FORM	ATIO	n Fo	R SE	O ID	NO:	70:						
30			,-	,													
		(	i) S	EQUE	NCE	CHAR	ACTE	RIST	ICS:								
							1 ba	_	airs								
							ic a		_								
35							S: s inea	_	.e								
33			(D)	101	Опос	11. 1	11100	-									
			ii)				E: c	DNA									
		(	ix)	FEAT	URE:												
40			(A	) NA	ME/K	ŒΥ:	Codi	ng S	Seque	ence							
							1	_	_								
			(I	ro (c	HER	INFO	RMAI	: NOI	:								
			(xi)	SEOI	· IENICE	י אר	CDTE	ירד∩ו	J. SI	EQ II	) NO	- 70 -					
45		,	(XI)	SEQU	ENCE	, DEC	CKI	1101	N. DI	JQ II	NO	. ,					
	ATO	AGO	GAC	GTO	GCT	r att	GTC	AA E	GAG	G GG	r TG	G CT	G CA	CAA	A CG	A GGG	48
	Met	. Sei	. Asp	val	l Ala	a Ile	e Val	Ly	s Glu		r Tr	p Lei	u Hi	s Ly		g Gly	
	1				5					10					15		
50	GDC	: ጥል(	י אינ	ומב ב	ב ארנ	т тас	a cec	G CC	A CG	C TAC	rr.	C CT	C CT	CAA	g AA	T GAT	96
00																n Asp	
		-		20		_			25	_				30			
	~~	, , , , , , ,	a mm	יים א	n	— πι <b>λ</b> ε	ית היי	יעט ב	G 00	G GG	ם כי	פ כ״	ጥ ርም	פ פא	ר פא	A CGT	144
55																n Arg	
55	J.	7	35			4 - X ·	<i>-</i> , .	40		J			45		-	_	
																	1

-						GCG Ala					192	
5						ATC Ile					240	)
10						GTG Val 90					288	ì
15	 					GTG Val					336	;
20						TCG Ser					384	Ė
25						CTG Leu					432	2
						AAG Lys					480	)
30						AAG Lys 170					528	3
35						ATC Ile					570	5
40	 	-				CTG Leu					624	4
45						CAG Gln					67	2
	Val						Phe			TCC Ser 240	72	0
50										GAG Glu	76	8
55			Leu			Ser			Val	TAC Tyr	81	6

F			CTC Leu 275														864
5			ACA Thr														912
10			AAG Lys														960
15			GAC Asp														1008
20			ATG Met														1056
25			GAG Glu 355														1104
20	CCG Pro	CGC Arg 370	ACG Thr	CTT Leu	GGT Gly	CCC Pro	GAG Glu 375	GCC Ala	AAG Lys	TCC Ser	TTG Leu	CTT Leu 380	Ser	GGG Gly	CTG Leu	CTC Leu	1152
30	AAG Lys 385	Lys	GAC Asp	CCC Pro	AAG Lys	CAG Gln 390	AGG Arg	CTT Leu	GGC	GGG Gly	GGC Gly 395	Ser	GAG Glu	GAC Asp	GCC Ala	AAG Lys 400	1200
35			ATG Met			Arg					Ile					Val	1248
40			AAG Lys		Leu					Lys					Ser		1296
45			ACC Thr	Arg					ı Glu					Met			1344
45			Pro					Ası					s Val			GAG Glu	1392
50	CG( Arg 46!	g Arg	G CCC	C CAC	TTO Phe	C CCC Pro 470	Gl:	TTO	C TCC	TAC	C TCC r Se: 47.	r Al	C AGO	C AGO	C ACC	GCC Ala 480	1440
55	TC:	G GAT	r CC! p Pro	A CCC	G GT( O Va:	l Ala	C AC	C AT	G GT	G AG 1 Se 49	r Ly	G GG s Gl	C GAG	G GAG	G CTO	G TTC u Phe 5	1488

5	ACC Thr	GGG Gly	GTG Val	GTG Val 500	CCC Pro	ATC Ile	CTG Leu	GTC Val	GAG Glu 505	CTG Leu	GAC Asp	GGC Gly	GAC Asp	GTA Val 510	AAC Asn	GGC Gly	1536
·	CAC His	AAG Lys	TTC Phe 515	AGC Ser	GTG Val	TCC Ser	GGC Gly	GAG Glu 520	GGC Gly	GAG Glu	GGC Gly	GAT Asp	GCC Ala 525	ACC Thr	TAC Tyr	GGC Gly	1584
10	AAG Lys	CTG Leu 530	ACC Thr	CTG Leu	AAG Lys	TTC Phe	ATC Ile 535	TGC Cys	ACC Thr	ACC Thr	GGC Gly	AAG Lys 540	CTG Leu	CCC Pro	GTG Val	CCC Pro	1632
15	TGG Trp 545	CCC Pro	ACC Thr	CTC Leu	GTG Val	ACC Thr 550	ACC Thr	CTG Leu	ACC Thr	TAC Tyr	GGC Gly 555	GTG Val	CAG Gln	TGC Cys	TTC Phe	AGC Ser 560	1680
20	Arg	TAC Tyr	Pro	Asp	His 565	Met	Lys	Gln	His	Asp 570	Phe	Phe	Lys	Ser	Ala 575	Met	1728
25	Pro	GAA Glu	Gly	Tyr 580	Val	Gln	Glu	Arg	Thr 585	Ile	Phe	Phe	Lys	Asp 590	Asp	Gly	1776
	Asn	TAC Tyr	Lys 595	Thr	Arg	Ala	Glu	Val 600	Lys	Phe	Glu	Gly	Asp 605	Thr	Leu	Val	1824
30	Asn	CGC Arg 610	Ile	Glu	Leu	Lys	Gly 615	Ile	Asp	Phe	Lys	Glu 620	Asp	Gly	Asn	Ile	1872
35	Leu 625	GGG Gly	His	Lys	Leu	Glu 630	Tyr	Asn	Tyr	Asn	Ser 635	His	Asn	Val	Tyr	Ile 640	1920
40	Met	GCC Ala	Asp	Lys	Gln 645	Lys	Asn	Gly	Ile	Lys 650	Val	Asn	Phe	Lys	Ile 655	Arg	1968
45	His	AAC Asn	Ile	Glu 660	Asp	Gly	ser.	Val	Gln 665	Leu	Ala	Asp	His	Tyr 670	Gln	Gln	2016
	AAC Asn	ACC Thr	CCC Pro 675	ATC Ile	GGC Gly	GAC Asp	GGC Gly	CCC Pro 680	GTG Val	CTG Leu	CTG Leu	CCC Pro	GAC Asp 685	AAC Asn	CAC His	TAC Tyr	2064
50	CTG Leu	AGC Ser 690	ACC Thr	CAG Gln	TCC Ser	GCC Ala	CTG Leu 695	AGC Ser	AAA Lys	GAC Asp	CCC Pro	AAC Asn 700	GAG Glu	AAG Lys	CGC Arg	GAT Asp	2112
55	CAC His 705	ATG Met	GTC Val	CTG Leu	CTG Leu	GAG Glu 710	TTC Phe	GTG Val	ACC Thr	GCC Ala	GCC Ala 715	GGG Gly	ATC Ile	ACT Thr	CTC Leu	GGC Gly 720	2160

ATG GAC GAG CTG TAC AAG TAA 2181 Met Asp Glu Leu Tyr Lys 725 5 (2) INFORMATION FOR SEQ ID NO:71: (i) SEQUENCE CHARACTERISTICS: 10 (A) LENGTH: 726 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 15 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71: 20 Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg 25 40 Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys 55 Thr Glu Arg Pro Arg Pro Asn Thr Phe Ile Ile Arg Cys Leu Gln Trp 30 Thr Thr Val Ile Glu Arg Thr Phe His Val Glu Thr Pro Glu Glu Arg Glu Glu Trp Thr Thr Ala Ile Gln Thr Val Ala Asp Gly Leu Lys Lys 105 Gln Glu Glu Glu Met Asp Phe Arg Ser Gly Ser Pro Ser Asp Asn 35 120 125 Ser Gly Ala Glu Glu Met Glu Val Ser Leu Ala Lys Pro Lys His Arg 135 Val Thr Met Asn Glu Phe Glu Tyr Leu Lys Leu Leu Gly Lys Gly Thr 150 155 40 Phe Gly Lys Val Ile Leu Val Lys Glu Lys Ala Thr Gly Arg Tyr Tyr 165 170 Ala Met Lys Ile Leu Lys Lys Glu Val Ile Val Ala Lys Asp Glu Val 180 185 Ala His Thr Leu Thr Glu Asn Arg Val Leu Gln Asn Ser Arg His Pro 45 Phe Leu Thr Ala Leu Lys Tyr Ser Phe Gln Thr His Asp Arg Leu Cys 215 Phe Val Met Glu Tyr Ala Asn Gly Gly Glu Leu Phe Phe His Leu Ser 50 Arg Glu Arg Val Phe Ser Glu Asp Arg Ala Arg Phe Tyr Gly Ala Glu 250 Ile Val Ser Ala Leu Asp Tyr Leu His Ser Glu Lys Asn Val Val Tyr 265 Arg Asp Leu Lys Leu Glu Asn Leu Met Leu Asp Lys Asp Gly His Ile 55 280

158

Lys Ile Thr Asp Phe Gly Leu Cys Lys Glu Gly Ile Lys Asp Gly Ala

		290					295					300				
	Thr		Lys	Thr	Phe	Cys	Gly	Thr	Pro	Glu	Tyr		Ala	Pro	Glu	Val
	305		_			310	_				315					320
5	Leu	Glu	Asp	Asn	Asp 325	Tyr	Gly	Arg	Ala	Val 330	Asp	Trp	Trp	Gly	Leu 335	Gly
	Val	Val	Met	Tyr 340	Glu	Met	Met	Cys	Gly 345	Arg	Leu	Pro	Phe	Tyr 350	Asn	Gln
	Asp	His	Glu 355	Lys	Leu	Phe	Glu	Leu 360	Ile	Leu	Met	Glu	Glu 365	Ile	Arg	Phe
10	Pro	Arg 370	Thr	Leu	Gly	Pro	Glu 375	Ala	Lys	Ser	Leu	Leu 380	Ser	Gly	Leu	Leu
	Lys 385	Lys	Asp	Pro	Lys	Gln 390	Arg	Leu	Gly	Gly	Gly 395	Ser	Glu	Asp	Ala	Lys 400
		Ile	Met	Gln	His	Arg	Phe	Phe	Ala	Gly	Ile	Val	Trp	Gln	His	Val
15					405					410					415	
	Tyr	Glu	Lys	Lys 420	Leu	Ser	Pro	Pro	Phe 425	Lys	Pro	Gln	Val	Thr 430	Ser	Glu
		•	435	_	_		Asp	440					445			
20		450			_		Asp 455	_				460		_		
		Arg	Pro	His	Phe		Gln	Phe	Ser	Tyr		Ala	Ser	Ser	Thr	
	465	λcn	Dro	Dro	V-1	470	Thr	Met	TeV	Car	475	Glv	Glu	Glu	T.en	480 Phe
25	361	Asp	210	110	485	ALU	1111	rice	Val	490	БУЗ	Cry	OIU	014	495	
	Thr	Gly	Val	Val 500	Pro	Ile	Leu	Val	Glu 505	Leu	Asp	Gly	Asp	Val 510	Asn	Gly
	His	Lys	Phe 515	Ser	Val	Ser	Gly	Glu 520	Gly	Glu	Gly	Asp	Ala 525	Thr	Tyr	Gly
30	Lys	Leu 530	Thr	Leu	Lys	Phe	Ile 535	Cys	Thr	Thr	Gly	Lys 540	Leu	Pro	Val	Pro
		Pro	Thr	Leu	Val		Thr	Leu	Thr	Tyr	_	Val	Gln	Cys	Phe	Ser
	545	<b>π</b> ~	Dro	) an	uic	550	Lys	Gln.	uic	7	555	Dhe	Lare	Ser	Δla	560 Met
35	_	_			565					570					575	Gly
				580					585					590		
			595					600	_				605			Val
40		610					615					620				Ile
	Leu 625	-	His	Lys	Leu	Glu 630	Tyr	Asn	Tyr	Asn	Ser 635		Asn	Val	Tyr	Ile 640
45			Asp	Lys	Gln 645		Asn	Gly	Ile	Lys 650	Val		Phe	Lys	Ile 655	Arg
	His	Asn	Ile	Glu 660	Asp	Gly	Ser	Val	Gln 665	Leu		Asp	His	Tyr 670	Gln	Gln
	Asn	Thr	Pro 675			Asp	Gly	Pro 680	Val		Leu	Pro	Asp	Asn	_	Tyr
50	Leu	Ser 690	Thr	Gln	Ser	Ala	Leu 695	Ser		Asp	Pro	Asn 700	Glu		Arg	Asp
	His 705	Met		Leu	Leu	Glu 710	Phe		Thr	Ala	Ala 715	Gly		Thr	Leu	Gly 720
55			Glu	Leu	Tyr 725	Lys										

## (2) INFORMATION FOR SEQ ID NO:72:

5	(:	(B) (C)	EQUEN LENC TYPI STRA TOPO	E: nu ANDEI	2751 aclei ONESS	bas c ac	se pa cid ingle	airs					
10		ii) N ix) I			TYPE	E: cI	ANC						
15	(2	(B)	NAM LOC OTH	CATIO	ON: ] INFOR	RMAT	2748 CON:	_	NO: 7	72:			
20		GAC Asp											48
25		CGC Arg											96
25		AAA Lys 35											144
30		AGC Ser											192
35		TGC Cys											240
40		ACG Thr											288
45		AGG Arg											336
40		TGT Cys 115											384
50		AAA Lys											432
55		GAC Asp											480

5							ACT Thr								528
3							CCT Pro 185								576
10							ATC Ile								624
15							TCC Ser								672
20							CCT Pro								720
25							CGG Arg								768
20							GAG Glu 265								816
30							GAA Glu								864
35						Glu	GGC Gly							AAG Lys	912
40	Glu									Lys				Pro 320	960
45					Gln				Leu					CTC Leu	1008
45				Phe				Gly					: Gly	AAG Lys	1056
50			Ala				/ Thr					Ala		AAG Lys	1104
55		Lys				Ile					Va]			C ACC 5 Thr	1152

5	ATG Met 385																1200
J	ACA Thr																1248
10	ATG Met																1296
15	GGG Gly																1344
20				TTC Phe													1392
25				AAT Asn													1440
				ATG Met													1488
30																TAC Tyr	1536
35				Gly					Trp					Val		CTG Leu	1584
40			Met					Pro					Glu			GAT Asp	1632
45		Leu					Met					Ser				TCC Ser 560	1680
40						val					Gly					CAG Gln	1728
50					, Lei					Gli					va.	AGA L Arg	1776
55				a Phe					e Ası					ı Glı		C AGG n Arg	1824

5								GGC Gly 620				1872
								GTC Val				1920
10						_	_	GAT Asp				1968
15								TTG Leu				2016
20								ACT Thr				2064
25								CAA Gln 700				2112
								AAA Lys				2160
30			_				_	TGG Trp	_		<b>-</b>	2208
35	_		_	_	_			AGA Arg				2256
40								CCC			GTA Val	2304
45								AAC Asn 780				2352
, -								AAT Asn			TTA Leu 800	2400
50								CTT Leu				2448
55							Tyr			Lys	CCA Pro	2496

164

									AAA Lys								2544
5																	
									TAT Tyr								2592
	GLY	850	vaı	GIII	neu	Ата	855	птэ	TYL	GIII	GIII	860	TIIL	PLO	TIE	GIÀ	
10									AAC								2640
	_	Gly	Pro	Val	Leu		Pro	Asp	Asn	His	•	Leu	Ser	Thr	Gln		
	865					870					875					880	
	GCC	CTT	TCC	AAA	GAT	CCC	AAC	GAA	AAG	AGA	GAT	CAC	ATG	ATC	CTT	CTT	2688
15	Ala	Leu	Ser	Lys	qaA	Pro	Asn	Glu	Lys	Arg	Asp	His	Met	Ile	Leu	Leu	
					885					890					895		
	GAG	ттт	GTA	ACA	GCT	GCT	GGG	ΔΥΥT	ACA	CAT	GGC	ΔTG	GAT	GAA	СТА	TAC	2736
									Thr								2,50
20				900			-		905		•		-	910		-	
	222	O O O	an a	a. a													0001
			CAG Gln		TAA												2751
	<i></i> 75	110	915	010													
25																	
			(2)	TNI	ZODM:	ישרטי	T EOI	0.00		NO. 1	7.0						
			(2)	TIVI	ORM	ALTOI	N FOI	K SE(	O ID	NO:	/3:						
		( :	i) si	EQUE	NCE (	CHAR	ACTE	RIST	ICS:								
30								no a	cids								
						nino											
						DNES: Y: 1:		ingle r	€							•	
			(2)	1010	5200			-									
35							_	rote									
		7)	/) F1	RAGMI	ENT '	TYPE	: in	tern	al								
		(2	ki) S	SEOUI	ENCE	DES	CRIP	TTON	: SE	ат с	NO:	73:					
		,-	,							2 12		, , ,					
40		Ala	Asp	Val	_	Pro	Ala	Asn	Asp		Thr	Ala	Ser	Gln		Val	
	ו גרא	λαη	7 ~~	Dho	5 הוא	7/~~~	T	<b>~1</b>	77.	10	7	~1 <b>~</b>	Y	n an	15	Uio	
	Ala	ASII	Arg	20	Ald	Arg	цуѕ	GIY	Ala 25	ьeu	Arg	GIII	пув	30	Val	птэ	
	Glu	Val	Lys		His	Lys	Phe	Ile	Ala	Arg	Phe	Phe	Lys		Pro	Thr	
45			35					40		_			45				
	Phe		Ser	His	Cys	Thr		Phe	Ile	Trp	Gly		Gly	Lys	Gln	Gly	
	Phe	50 Gln	Cvs	Gln	Val	Cvs	55 Cvs	Dhe	Val	V = 1	Wie	60 1.v≈	Δτα	Cvs	His	Glu	
	65	<b>U</b>	CID	0141	• • •	70	СуБ	1 110	Val	Val	75	цуз	n. g	Cys	1110	80	
50	Phe	Val	Thr	Phe	Ser	Cys	Pro	Gly	Ala	Asp	Lys	Gly	Pro	Asp	Thr	Asp	
				<b>a</b> -	85		_		-	90	•	<b></b>	_	~-	95		
	Asp	Pro	Arg	Ser		Hls	ьys	Phe	Ьуs 105		His	Thr	туг	Gly 110		Pro	
	Thr	Phe	Cys			Cys	Glv	Ser			Tyr	Glv	Leu			Gln	
55			115			-	- 4	120			•	•	125				
	Gly	Met	Lys	Cys	Asp	Thr	Cys	Asp	Met	Asn	Val	His	Asn	Gln	Cys	Val	

		120					125					3.40				
	Tla	130	λαη	Dro	Car	T.011	135 Cvs	Gly	Mat	λcn	Wie	140	G) v	Lare	λ·κα	G) v
	145	VPII	rap	PIO	Ser	150	Cys	GTĀ	Mec	nap	155	1111	GIU	цуз	n. 9	160
		Tle	Tvr	T.em	Lvg		Glu	Val	Thr	Aen		Lvg	Len	His	Val	
5			-1-	200	165			•		170		-7-			175	
Ū	Val	Arq	Asp	Ala		Asn	Leu	Ile	Pro	-	Asp	Pro	Asn	Glv		Ser
	•		•	180	3		-	_	185		•			190		
	Asp	Pro	Tyr	Val	Lys	Leu	Lys	Leu	Ile	Pro	Asp	Pro	Lys	Asn	Glu	Ser
	_		195		_		_	200			_		205			
10	Lys	Gln	Lys	Thr	Lys	Thr	Ile	Arg	Ser	Asn	Leu	Asn	Pro	Gln	Trp	Asn
		210					215					220				
	Glu	Ser	Phe	Thr	Phe	_	Leu	ГÀЗ	Pro	Ser		Lys	Asp	Arg	Arg	
	225	_	_	_		230					235					240
4.5	Ser	Val	Glu	Ile		Asp	Trp	Asp	Arg		Thr	Arg	Asn	Asp		Met
15		_	_	_	245	~1		<b>a</b> .	~1	250				<b>5</b>	255	
	GIY	ser	ьeu		Pne	GIĄ	vai	Ser		Leu	Met	гуѕ	мес		АТА	ser
	C1.,	Trn	The case	260	ח ז ח	ui a	N an	Gln	265	C1	Clv	C1.,	Tree	270	λαη	Wal
	GIY	rrp	275	шуъ	MIG	urs	Wali	280	Giu	GIU	GTÅ	GIU	285	TYL	Wali	vai
20	Dro	Tle		Glu	Glv	Asn	Glu	Glu	Glv	Δsn	Met	Glu		Δra	Gln	Lvs
20	110	290	110	Olu	O <sub>I</sub>	пор	295	014	O ± 7	11011		300	шец	*****9	0111	27.5
	Phe		Lvs	Ala	Lvs	Leu		Pro	Val	Glv	Asn		Val	Ile	Ser	Pro
	305		-1-		-,-	310	1			1	315	-1-				320
	Ser	Glu	Asp	Arg	Lys	Gln	Pro	Ser	Asn	Asn	Leu	Asp	Arg	Val	Lys	Leu
25			_	_	325					330		_			335	
	Thr	Asp	Phe	Asn	Phe	Leu	Met	Val	Leu	Gly	Lys	Gly	Ser	Phe	Gly	Lys
				340					345					350		
	Val	Met	Leu	Ala	Asp	Arg	Lys	Gly	Thr	Glu	Glu	Leu	_	Ala	Ile	Lys
			355					360	_				365			
30	Ile		Lys	Lys	Asp	Val		Ile	Gln	Asp	Asp		Val	Glu	Cys	Thr
		370	a1	•	<b>3</b>	**- 1	375	<b>3</b> 3-	<b>.</b>	<b>T</b>		380	D	7	nh -	7
		vai	GIU	гÀг	Arg		ьeu	AIA	Leu	ьeu		гăг	Pro	Pro	Pne	Leu
	385	Gl n	Len	Uic	Ca~	390	Dhe	Gln	Thr	1751	395	7~~	Len	ጥረም	Dhe	400 Val
35	1111	Gili	Бец	птэ	405	Cys	PIIC	GIII	TIIL	410	Чар	ALG	neu	TYL	415	vai
00	Met	Glu	Tvr	Val		Glv	Glv	Asp	Leu		Tvr	His	Tle	Gln		Val
			-1-	420		1	1		425		-1-			430		
	Gly	Lys	Phe	Lys	Glu	Pro	Gln	Ala	Val	Phe	Tyr	Ala	Ala	Glu	Ile	Ser
	-	-	435	•				440			•		445			
40	Ile	Gly	Leu	Phe	Phe	Leu	His	Lys	Arg	Gly	Ile	Ile	Tyr	Arg	Asp	Leu
		450					455					460				
	Lys	Leu	Asn	Asn	Val	Met	Leu	Asn	Ser	Glu	Gly	His	Ile	Lys	Ile	Ala
	465					470					475					480
	Asp	Phe	Gly	Met	_	Lys	Glu	His	Met			Gly	Val	Thr		Arg
45			_		485		_			490					495	_
	Thr	Phe	Cys	_		Pro	Asp	Tyr		Ala	Pro	Glu	IIe			Tyr
	<b>~1</b> -	D===	M	500		0	17 1	7	505	-	n 1		<b>~1</b>	510		T 033
	GIII	PIO	515	_	гÀг	ser	vai	520	irp	rrp	Ата	TYL	525		ьец	Leu
50	Тчт	Clu			ת ו ת	Glaz	Gln		Dro	Dhe	λcn	Glv			Glu	Asp
30	TYL	530		пец	Ата	СТУ	535		PIO	FIIC	Asp	540		. ASP	GIU	Asp
	G3 11			G3 n	Ser	IJe			His	Asn	Val			Pro	Lvs	Ser
	545					550					555		- <i>1</i> -		_1 2	560
			Lys	Glu	Ala			Ile	Cys	Lys			Met	Thr	Lys	Gln
55			•		565				•	570					575	
	Pro	Ala	Lys	Arg	Leu	Gly	Cys	Gly	Pro	Glu	Gly	Glu	Arg	Asp	Val	Arg

166

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585
                  580
     Glu His Ala Phe Phe Arg Arg Ile Asp Trp Glu Lys Leu Glu Asn Arg
                                  600
     Glu Ile Gln Pro Pro Phe Lys Pro Lys Val Cys Gly Lys Gly Ala Glu
5
                              615
                                                  620
     Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro
                          630
                                              635
      Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe
                      645
                                          650
      Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val
10
      Gly Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro
                                  680
      Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val
15
                              695
                                                   700
      Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys
                                               715
                          710
      Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val
                                           730
                      725
      Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His
20
                                       745
                  740
      Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val
                                  760
                                                       765
      Gln Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg
25
                               775
      Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu
                                               795
      Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met
                                           810
                       805
      Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro
30
                                      825
      Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp
                                  840
      Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly
35
                               855
      Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser
                           870
                                               875
      Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu
                                           890
      Glu Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr
40
                                       905
      Lys Pro Gln Glu
               915
45
                (2) INFORMATION FOR SEQ ID NO:74:
             (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 2157 base pairs
               (B) TYPE: nucleic acid
               (C) STRANDEDNESS: single
50
               (D) TOPOLOGY: linear
             (ii) MOLECULE TYPE: cDNA
```

(A) NAME/KEY: Coding Sequence

(ix) FEATURE:

167

(B) LOCATION: 1...2154(D) OTHER INFORMATION:

## (xi) SEQUENCE DESCRIPTION: SEO ID NO:74:

5		()	(i) S	EQUE	ENCE	DESC	RIPT	: MOI	SEC	) ID	NO: 7	74:					
				ATC													48
	Met 1	Ser	Ser	Ile	Leu 5	Pro	Phe	Thr	Pro	Pro 10	Val	Val	Lys	Arg	Leu 15	Leu	
10	GGA	TGG	AAG	AAG	TCA	GCT	GGT	GGG	TCT	GGA	GGA	GCA	GGC	GGA	GGA	GAG	96
				Lys 20													
15				CAG Gln													144
			35					40					45	_			
				CTA													192
20	val	50	пÀа	Leu	ьуs	ьуs	55	GIÀ	Arg	Leu	Asp	60	Leu	GIU	ьys	Ala	
				CAA													240
	Ile 65	Thr	Thr	Gln	Asn	Cys 70	Asn	Thr	Lys	Cys	Val 75	Thr	Ile	Pro	Ser	Thr 80	
25																	_
				ATT Ile													288
	-3-				85	1				90					95		
30	GAT	ACA	ACA	GGC	CTT	TAC	AGC	TTC	TCT	GAA	CAA	ACC	AGG	TCT	CTT	GAT	336
	Asp	Thr	Thr	Gly 100	Leu	Tyr	Ser	Phe	Ser 105	Glu	Gln	Thr	Arg	Ser 110	Leu	Asp	
	GGT	CGT	CTC	CAG	GTA	TCC	CAT	CGA	AAA	GGA	TTG	CCA	CAT	GTT	ATA	TAT	384
35	Gly	Arg	Leu 115	Gln	Val	Ser	His	Arg 120	Lys	Gly	Leu	Pro	His 125	Val	Ile	Tyr	
				TGG													432
40	Суз	Arg 130	Leu	Trp	Arg	Trp	Pro 135	Asp	Leu	His	Ser	His 140	His	Glu	Leu	Lys	
				AAC													480
	Ala 145	Ile	Glu	Asn	Cys	Glu 150	Tyr	Ala	Phe	Asn	Leu 155	Lys	Lys	Asp	Glu	Val 160	
45																	
				CCT Pro													528
	Cys	vai	ASII	FIO	165	UIS	TYL	GIII	ALG	170	Giu	THE	PIO	Val	175	PIO	
50				GTG													576
	Pro	Val	Leu	Val 180	Pro	Arg	His	Thr	Glu 185	Ile	Leu	Thr	Glu	Leu 190	Pro	Pro	
r.				TAT													624
55	Leu	qaA	Asp 195	Tyr	Thr	His	Ser	Ile 200	Pro	Glu	Asn	Thr	Asn 205	Phe	Pro	Ala	

5	GGA Gly																672
3												CAG Gln					720
10												ACT Thr					768
15												TAC Tyr					816
20												CAG Gln					864
25												GAT Asp 300					912
												CTC Leu					960
30						Glu						ATA Ile				Val	1008
35					Ile					Phe					Ser	GAT Asp	1056
40				Phe					Asn					Tyr		TGG Trp	1104
45			Ala					Il€					Asn			ATC Ile	1152
40		Asr					Ala					a Glr				CAG Gln 400	1200
50						Туг					g Met					A ATG g Met	1248
55					Gly					туз					r Va	A ACA l Thr	1296

5									CTA Leu	_		1344
J									CGT Arg			1392
10	 								GCC Ala			1440
15									ATC Ile			1488
20	-								TCC Ser 510			1536
25									TTC Phe	_		1584
									ACC Thr			1632
30									ATG Met			1680
35									CAG Gln			1728
40									GCC Ala 590	_	_	1776
45									AAG Lys			1824
								Leu	GAG Glu			1872
50	 Asn	 	 	Tyr	 	 	Lys		AAG Lys		GGC Gly 640	1920
55			Lys			Ile			GGC			1968

5			GCC Ala														2016
-			CTG Leu 675														2064
10			CCC Pro														2112
15		_	GCC Ala				_								TAA		2157
20		(:	i) SI (A)		NCE (	CHAR! 718	ACTE amin	RIST:		NO : 7	75:						
25		( -	(C)	STR!	ANDEI OLOG!	ONESS (: 1:	S: s: inear	ingle c									
			v) FI														
30			xi) s														
30	1	Ser	Ser	Ile	Leu 5	Pro	Phe	Thr	Pro	Pro 10	Val	Val	_		15		
30 35	1 Gly	Ser Trp	Ser Lys	Ile Lys 20	Leu 5 Ser	Pro Ala	Phe Gly	Thr	Pro Ser 25	Pro 10 Gly	Val Gly	Val Ala	Gly	Gly 30	15 Gly	Glu	
	l Gly Gln	Ser Trp Asn	Ser Lys Gly 35	Ile Lys 20 Gln	Leu 5 Ser Glu	Pro Ala Glu	Phe Gly Lys	Thr Gly Trp 40	Pro Ser 25 Cys	Pro 10 Gly Glu	Val Gly Lys	Val Ala Ala	Gly Val 45	Gly 30 Lys	15 Gly Ser	Glu Leu	
35	1 Gly Gln Val	Ser Trp Asn Lys 50	Ser Lys Gly 35 Lys	Ile Lys 20 Gln Leu	Leu 5 Ser Glu Lys	Pro Ala Glu Lys	Phe Gly Lys Thr	Thr Gly Trp 40 Gly	Pro Ser 25 Cys Arg	Pro 10 Gly Glu Leu	Val Gly Lys Asp	Val Ala Ala Glu 60	Gly Val 45 Leu	Gly 30 Lys Glu	15 Gly Ser Lys	Glu Leu Ala	
	1 Gly Gln Val Ile 65	Ser Trp Asn Lys 50 Thr	Ser Lys Gly 35 Lys Thr	Ile Lys 20 Gln Leu Gln	Leu 5 Ser Glu Lys Asn	Pro Ala Glu Lys Cys 70	Phe Gly Lys Thr 55 Asn	Thr Gly Trp 40 Gly Thr	Pro Ser 25 Cys Arg	Pro 10 Gly Glu Leu Cys	Val Gly Lys Asp Val	Val Ala Ala Glu 60 Thr	Gly Val 45 Leu Ile	Gly 30 Lys Glu Pro	15 Gly Ser Lys Ser	Glu Leu Ala Thr	
35	1 Gly Gln Val Ile 65 Cys	Ser Trp Asn Lys 50 Thr	Ser Lys Gly 35 Lys Thr	Ile Lys 20 Gln Leu Gln Ile	Leu 5 Ser Glu Lys Asn Trp	Pro Ala Glu Lys Cys 70 Gly	Phe Gly Lys Thr 55 Asn Leu	Thr Gly Trp 40 Gly Thr	Pro Ser 25 Cys Arg Lys	Pro 10 Gly Glu Leu Cys Pro 90	Val Gly Lys Asp Val 75 Asn	Val Ala Ala Glu 60 Thr	Gly Val 45 Leu Ile	Gly 30 Lys Glu Pro	15 Gly Ser Lys Ser Gln 95	Glu Leu Ala Thr 80 Trp	
35	1 Gly Gln Val Ile 65 Cys	Ser Trp Asn Lys 50 Thr Ser	Ser Lys Gly 35 Lys Thr Glu	Lys 20 Gln Leu Gln Ile Gly 100	Leu 5 Ser Glu Lys Asn Trp 85 Leu	Pro Ala Glu Lys Cys 70 Gly Tyr	Phe Gly Lys Thr 55 Asn Leu Ser	Thr Gly Trp 40 Gly Thr Ser	Pro Ser 25 Cys Arg Lys Thr Ser 105	Pro 10 Gly Glu Leu Cys Pro 90 Glu	Val Gly Lys Asp Val 75 Asn	Val Ala Ala Glu 60 Thr Thr	Gly Val 45 Leu Ile Ile Arg	Gly 30 Lys Glu Pro Asp Ser 110	Ser Lys Ser Gln 95 Leu	Glu Leu Ala Thr 80 Trp Asp	
35 40	1 Gly Gln Val Ile 65 Cys Asp	Ser Trp Asn Lys 50 Thr Ser Thr	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val	Pro Ala Glu Lys Cys 70 Gly Tyr Ser	Phe Gly Lys Thr 55 Asn Leu Ser	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys	Pro 10 Gly Glu Leu Cys Pro 90 Glu	Val Gly Lys Asp Val 75 Asn Gln Leu	Val Ala Ala Glu 60 Thr Thr	Gly Val 45 Leu Ile Ile Arg His	Gly 30 Lys Glu Pro Asp Ser 110 Val	Ser Lys Ser Gln 95 Leu	Glu Leu Ala Thr 80 Trp Asp	
35 40 45	1 Gly Gln Val Ile 65 Cys Asp Gly	Ser Trp Asn Lys 50 Thr Ser Thr Arg Arg 130	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115 Leu	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln Trp	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val Arg	Pro Ala Glu Lys Cys 70 Gly Tyr Ser Trp	Phe Gly Lys Thr 55 Asn Leu Ser His Pro	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120 Asp	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys	Pro 10 Gly Glu Leu Cys Pro 90 Glu Gly His	Val Gly Lys Asp Val 75 Asn Gln Leu Ser	Val Ala Ala Glu 60 Thr Thr Pro His 140	Gly Val 45 Leu Ile Ile Arg His 125	Gly 30 Lys Glu Pro Asp Ser 110 Val	Ser Lys Ser Gln 95 Leu Ile	Glu Leu Ala Thr 80 Trp Asp Tyr Lys	
35 40	1 Gly Gln Val Ile 65 Cys Asp Gly Cys Ala 145	Ser Trp Asn Lys 50 Thr Ser Thr Arg Arg 130 Ile	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115 Leu Glu	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln Trp Asn	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val Arg Cys	Pro Ala Glu Lys Cys 70 Gly Tyr Ser Trp Glu 150	Phe Gly Lys Thr 55 Asn Leu Ser His Pro 135	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120 Asp	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys Leu Phe	Pro 10 Gly Glu Leu Cys Pro 90 Glu Gly His	Val Gly Lys Asp Val 75 Asn Gln Leu Ser Leu 155	Val Ala Ala Glu 60 Thr Thr Thr Lys	Gly Val 45 Leu Ile Ile Arg His 125 His	Gly 30 Lys Glu Pro Asp Ser 110 Val Glu Asp	Ser Lys Ser Gln 95 Leu Ile Leu Glu	Glu Leu Ala Thr 80 Trp Asp Tyr Lys Val 160	
35 40 45	1 Gly Gln Val Ile 65 Cys Asp Gly Cys Ala 145 Cys	Ser Trp Asn Lys 50 Thr Ser Thr Arg Arg 130 Ile Val	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115 Leu Glu Asn	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln Trp Asn Pro	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val Arg Cys Tyr 165	Pro Ala Glu Lys Cys 70 Gly Tyr Ser Trp Glu 150 His	Phe Gly Lys Thr 55 Asn Leu Ser His Pro 135 Tyr	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120 Asp Ala Gln	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys Leu Phe Arg	Pro 10 Gly Glu Leu Cys Pro 90 Glu Gly His Asn Val	Val Gly Lys Asp Val 75 Asn Gln Leu Ser Leu 155 Glu	Val Ala Ala Glu 60 Thr Thr Thr Lys Thr	Gly Val 45 Leu Ile Ile Arg His 125 His	Gly 30 Lys Glu Pro Asp Ser 110 Val Glu Asp	Ser Lys Ser Gln 95 Leu Ile Glu Leu 175	Glu Leu Ala Thr 80 Trp Asp Tyr Lys Val 160 Pro	
35 40 45	1 Gly Gln Val Ile 65 Cys Asp Gly Cys Ala 145 Cys	Ser Trp Asn Lys 50 Thr Ser Thr Arg Arg 130 Ile Val	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115 Leu Glu Asn	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln Trp Asn Pro Val 180	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val Arg Cys Tyr 165 Pro	Pro Ala Glu Lys Cys 70 Gly Tyr Ser Trp Glu 150 His	Phe Gly Lys Thr 55 Asn Leu Ser His Pro 135 Tyr Tyr	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120 Asp Ala Gln Thr	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys Leu Phe Arg Glu 185	Pro 10 Gly Glu Leu Cys Pro 90 Glu Gly His Asn Val 170 Ile	Val Gly Lys Asp Val 75 Asn Gln Leu 155 Glu Leu	Val Ala Ala Glu 60 Thr Thr Thr Thr Pro His 140 Lys Thr	Gly Val 45 Leu Ile Ile Arg His 125 His Cys	Gly 30 Lys Glu Pro Asp Ser 110 Val Glu Asp Val Leu 190	Ser Lys Ser Gln 95 Leu Ile Glu Leu 175 Pro	Glu Leu Ala Thr 80 Trp Asp Tyr Lys Val 160 Pro	

			195					200					205			
	Gly	Ile 210		Pro	Gln	Ser	Asn 215		Ile	Pro	Glu	Thr 220		Pro	Pro	Gly
5	Tyr 225		Ser	Glu	Asp	Gly 230		Thr	Ser	Asp	Gln 235		Leu	Asn	Gln	Ser 240
	Met	Asp	Thr	Gly	Ser 245	Pro	Ala	Glu	Leu	Ser 250	Pro	Thr	Thr	Leu	Ser 255	Pro
	Val	Asn	His	Ser 260	Leu	qaA	Leu	Gln	Pro 265	Val	Thr	Tyr	Ser	Glu 270	Pro	Ala
10		_	275		Ile			280					285			
		290			Ser		295					300				
15		Ser	Asn	Ser	Glu	Arg 310	Phe	Cys	Leu	Gly	Leu 315	Leu	Ser	Asn	Val	Asn 320
13	305 Arq	Asn	Ala	Thr	Val		Met	Thr	Arg	Arg		Ile	Gly	Arg	Gly	
	_				325					330					335	
	_			340	Ile				345					350		
20	Ser	Ala	11e 355	Phe	Val	Gln	Ser	Pro 360	Asn	Cys	Asn	Gin	Arg 365	Tyr	GIY	Trp
	His	Pro 370	Ala	Thr	Val	Cys	Lys 375	Ile	Pro	Pro	Gly	Cys 380	Asn	Leu	Lys	Ile
25		Asn	Asn	Gln	Glu	Phe 390	Ala	Ala	Leu	Leu	Ala 395	Gln	Ser	Val	Asn	Gln 400
23	385 Gly	Phe	Glu	Ala	Val		Gln	Leu	Thr	Arg		Cys	Thr	Ile	Arg	
	_			_	405		<b>~</b> 1		<b>~</b> 3	410		<b>3</b>	<b>~</b> 1	mh aa	415	mh sa
20				420	Gly				425					430		
30			435		Trp			440					445			
	Leu	Asp 450	Lys	Val	Leu	Thr	G1n 455	Met	GTÀ	Ser	Pro	Ser 460	vai	Arg	cys	ser
25		Met	Ser	Trp	Val	Pro 470	Arg	Ala	Arg	Asp	Pro 475		Val	Ala	Thr	Met 480
35	465 Val	Ser	Lys	Gly	Glu 485		Leu	Phe	Thr	Gly	Val		Pro	Ile	Leu 495	
	Glu	Leu	Asp	Gly		Val	Asn	Gly	His			Ser	Val	Ser		Glu
40	<b>a</b> 1	<b>~1</b>	<b>01</b>	500		m1	m	<b>a</b> 1	505		mb	T 0.11	T	510		Cara
40	GIY	GIU	515		Ala	Thr	туг	520		Leu	THE	ьeu	. Був 525		116	Cys
	Thr	Thr 530	Gly	Lys	Leu	Pro	Val 535		Trp	Pro	Thr	Leu 540		Thr	Thr	Leu
A.E.		Tyr	Gly	Val	Gln	_		Ser	Arg	Tyr			His	Met	Lys	Gln 560
45	545 His	Asp	Phe	Phe	Lys 565			Met	Pro	Glu 570			Val	Gln	Glu 575	Arg
	Thr	Ile	Phe	Phe	Lys		Asp	Gly	Asn 585	Туг		Thr	Arg	Ala	Glu	Val
50	Lys	Phe	Glu 595	Gly		Thr	Leu	Val	Asn		Ile	Glu	Leu 605	Lys		Ile
	Asp	Phe 610	Lys		Asp	Gly	Asn 615	Ile		Gly	His	Lys 620	Leu		Tyr	Asn
55	Tyr 625	Asn		His	Asn	Val	Туг		Met	Ala	Asp 635	Lys		Lys	Asn	Gly 640
			Val	Asn	Phe	Lys	Ile	Arg	His	Asr	ıle	Glu	ı Asp	Gly	/ Ser	Val

									1	72								
					545				(	550				$\epsilon$	555			
	Gln I	Leu i	Ala			ryr (	3ln (	3ln A	Asn :	Thr I	ro 1	(le (			3ly I	?ro		
				660	<b>.</b>	<b>.</b> 7			665	30m 5	nh w C	מוד		570 11 = 1	.eu 9	Ser		
5	Val 1		Leu 675	Pro A	Asp A	Asn 1		191 .	beu i	ser i	ini c		585	31a 1	Jeu .	JC1		
3	Lys i			Asn (	Glu 1	Ĺуs i			His I	Met V	/al I	Leu I	Leu (	3lu 1	Phe '	Val		
	- (	690				(	695				7	700						
	Thr A	Ala .	Ala	Gly		Thr : 710	Leu (	Gly	Met .		31u 1 715	Leu :	ryr .	ьуs				
10	705					,10					, 13							
			(2)	INF	ORMA'	TION	FOR	SEQ	ID	NO:7	<b>5</b> :							
		/ 2	) SE	OTTEN.	CP C	. ת כז ת ז	Centro	TOTT	ce.									
		(1		LENG														
15				TYPE														
				STRA														
			(D)	TOPO	LOGY	: 11	near											
		(i	i) M	OLEC	ULE	TYPE	: cD	NA										
20		(i	.x) F	EATU	RE:													
			(A)	NAM	E/KE	Y : C	odin	ıa Se	guer	ce								
				LOC				_	1									
			(D)	OTH	ER I	NFOR	ITAM	: ИО										
25		(5	ci) S	SEOI IE	NCE	DESC	וים ד <b>קי</b> י	י מסדי	SEC	OID (	NO : 7	6:						
			TAA														48	
30		Asp	Asn	Met	Ser 5	Ile	Thr	Asn	Thr	Pro 10	Thr	Ser	Asn	Asp	15	Cys		
30	1				,													
	CTG	AGC	ATT	GTG	CAT	AGT	TTG	ATG	TGC	CAT	AGA	CAA	GGT	GGA	GAG	AGT	96	
	Leu	Ser	Ile		His	Ser	Leu	Met	Cys 25	His	Arg	Gin	GIY	30 GIA	GIU	ser		
35				20					23					50				
			TTT														144	
	Glu	Thr	Phe	Ala	Lys	Arg	Ala		Glu	Ser	Leu	Val	Lys 45	Lys	Leu	гàг		
			35					40					45					
40	GAG	AAA	AAA	GAT	GAA	TTG	GAT	TCT	TTA	ATA	ACA	GCT	ATA	ACT	ACA	TAA	192	
	Glu		Lys	Asp	Glu	Leu		Ser	Leu	Ile	Thr		Ile	Thr	Thr	Asn		
		50					55					60						
	GGA	GCT	CAT	CCT	AGT	AAA	TGT	GTT	ACC	ATA	CAG	AGA	ACA	TTG	GAT	GGG	240	
45		Ala	His	Pro	Ser		Cys	Val	Thr	Ile		Arg	Thr	Leu	Asp	Gly 80		
	65					70					75					50		
	AGG	CTT	CAG	GTG	GCT	GGT	CGG	AAA	GGA	TTT	CCT	CAT	GTG	ATC	TAT	GCC	288	
	Arg	Leu	Gln	Val		Gly	Arg	Lys	Gly		Pro	His	Val	Ile		Ala		
50					85					90					95			
	CGT	СТС	TGG	AGG	TGG	CCT	GAT	CTI	CAC	AAA	AAT	' GAA	CTA	AAA	CAI	GTT	336	
	Arg	Leu	Trp	Arg	Trp	Pro	Asp	Lev	ı His	Lys	Asn	Glu	Leu	Lys	His	val		
EE				100	•				105	i				110	,			
55	AAA	TAT	r TGI	CAC	TAT	GCG	TTI	GAO	TT	AAA A	TGI	GAT	' AGT	GTC	TG	r GTG	384	
																		172

									-	1/3							
	Lys	Tyr	Cys 1 <b>1</b> 5	Gln	Tyr	Ala	Phe	Asp 120	Leu	Lys	Cys	Asp	Ser 125	Val	Cys	Val	
5												GGA Gly 140					432
10												ATG Met					480
15												TTG Leu					528
10												AAT Asn					576
20												TCT Ser					624
25												GCT Ala 220					672
30												GGA Gly					720
35												GGA Gly				_	768
					His							TGG Trp					816
40				Tyr												CTT Leu	864
45			His					Pro					Tyr			GTT Val	912
50		Asn					Gln					Asn				CCT Pro 320	960
55						Ile					Met					GGA Gly	1008
55	GAG	ACA	TTI	' AAG	GTI	CCI	TCA	AGC	TGC	CCT	TTA ?	GTI	ACT	GTT	GAT	GGA	1056

									,	14							
	Glu	Thr		Lys 340	Val	Pro	Ser	Ser	Cys 345	Pro	Ile	Val	Thr	Val 350	Asp	Gly	
5									CGC Arg			Leu					1104
10									GAG Glu								1152
45									GGT Gly								1200
15									GTA Val								1248
20									GCT Ala 425								1296
25									CGT Arg								1344
30									GCA Ala								1392
25		Ala					Gly					Gly				CCA Pro 480	1440
35						Ala					Gly					CGT Arg	1488
40					Leu					Val					Pro	GAT Asp	1536
45				Gln					ı Thr					e Glu		CAC His	1584
50			Arg					Le					ı His			G CCG E Pro	1632
		e Ala					o Lev					o Pro				C ATG r Met 560	1680
55	GTO	G AGO	DAA C	G GGC	GA(	G GA	G CTO	3 TT	C AC	C GG	G GT	G GT	G CC	C AT	C CT	G GTC	1728

										175							
	Val	Ser	Lys	Gly	Glu 565	Glu	Leu	Phe	Thr	Gly 570	Val	Val	Pro	Ile	Leu 575	Val	
5			GAC Asp														1776
10			GGC Gly 595														1824
15			GGC Gly														1872
.0			GGC Gly														1920
20			TTC Phe														1968
25			TTC Phe														2016
30			GAG Glu 675														2064
0.5			AAG Lys										Leu				2112
35		Asn	AGC Ser									Lys					2160
40			GTG Val			Lys					Ile					Val	2208
45			GCC Ala		His					Thr					Gly		2256
50				Pro					Leu					Ala		G AGC 1 Ser	2304
			Pro					, Ast					ı Leu			C GTG e Val	2352
55	ACC	G GCC	GCC	: GGC	TA E	C ACI	CTC	GGC	C ATO	G GAC	GAC	G CTC	TAC	: AAC	3 TA	A	2397 17

176

Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
785 790 795

- 5 (2) INFORMATION FOR SEQ ID NO:77:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 798 amino acids
    - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

15

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

	Met 1	Asp	Asn	Met	Ser 5	Ile	Thr	Asn	Thr	Pro 10	Thr	Ser	Asn	Asp	Ala 15	Cys
20	Leu	Ser	Ile	Val 20	His	Ser	Leu	Met	Cys 25	His	Arg	Gln	Gly	Gly 30	Glu	Ser
	Glu	Thr	Phe 35	Ala	Lys	Arg	Ala	Ile 40	Glu	Ser	Leu	Val	Lys 45	Lys	Leu	Lys
25	Glu	Lys 50	Lys	Asp	Glu	Leu	Asp 55	Ser	Leu	Ile	Thr	Ala 60	Ile	Thr	Thr	Asn
	65					70					75			Leu		80
	_				85					90				Ile	95	
30	Arg	Leu	Trp	Arg 100	Trp	Pro	Asp	Leu	His 105	Lys	Asn	Glu	Leu	Lys 110	His	Val
	_		115					120					125	Val		
35		130					135					140		Asp		
	145					150					155			Val		160
		_			165					170				Thr	175	
40	His	Ser	Ile	Gln 180	Thr	Ile	Gln	His	Pro 185		Ser	Asn	Arg	Ala 190	Ser	Thr
	Glu	Thr	Tyr 195	Ser	Thr	Pro	Ala	Leu 200		Ala	Pro	Ser	Glu 205		Asn	Ala
45	Thr	Ser 210		Ala	Asn	Phe	Pro 215		Ile	Pro	Val	Ala 220		Thr	Ser	Gln
	225					230					235					Ile 240
			_		245					250					255	
50				260					265	5				270		Arg
			275					280	)				285	5		Leu
55		290	)				295	5				300	)			Val
	His	Asr	Glu	Leu	Ala	Phe	Glr	n Pro	Pro	o Ile	e Ser	Asr	n His	Pro	Ala	Pro

	305					310					315					320
			Trp	Сув	Ser 325			Tyr	Phe	Glu 330		Asp	Val	Gln		Gly
5	Glu	Thr	Phe	Lys 340		Pro	Ser	Ser			Ile	Val	Thr	Val	335 Asp	Gly
3	Tyr	Val			Ser	Gly	Gly		345 Arg	Phe	Cys	Leu		350 Gln	Leu	Ser
	Asn		355 His	Arg	Thr	Glu		360 Ile	Glu	Arg	Ala	Arg	365 Leu	His	Ile	Gly
10		370 Gly	Val	Gln	Leu		375 Cys	Lys	Gly	Glu	Gly	380 Asp	Val	Trp	Val	Arg
	385 Cys	Leu	Ser	Asp	His	390 Ala	Val	Phe	Val	Gln	395 Ser	Tvr	ጥህጕ	Leu	Asn	400 Ara
					405					410					415	
15				420					425					Tyr 430		
			435					440					445	Gln		
		450					455					460		Ala		
20	Val 465	Ala	Gly	Asn	Ile	Pro 470	Gly	Pro	Gly	Ser		Gly	Gly	Ile	Ala	
		Ile	Ser	Leu	Ser 485		Ala	Ala	Gly		475 Gly	Val	Asp	Asp		480 Arg
	Arg	Leu	Cys	Ile		Arg	Met	Ser	Phe	490 Val	Lys	Gly	Trp	Gly	495 Pro	Asp
25				500					505					510 Glu		
			515					520					525			
		530					535					540		Thr		
30	Ile 545	Ala	Asp	Pro	Gln	Pro 550	Leu	Asp	Trp	Asp	Pro 555	Pro	Val	Ala	Thr	Met 560
	Val	Ser	Lys	Gly	Glu 565	Glu	Leu	Phe	Thr	Gly 570	Val	Val	Pro	Ile	Leu 575	Val
35	Glu	Leu	Asp	Gly 580	Asp	Val	Asn	Gly	His 585		Phe	Ser	Val	Ser 590		Glu
	Gly	Glu	Gly 595	Asp	Ala	Thr	Tyr	Gly 600		Leu	Thr	Leu	Lys 605	Phe	Ile	Cys
	Thr		Gly	Lys	Leu	Pro			Trp	Pro	Thr	Leu		Thr	Thr	Leu
40	Thr	610 Tyr	Gly	Val	Gln	Cys	615 Phe	Ser	Arq	Tvr	Pro	620 Asp	His	Met	Lvs	Gln
	625					630					635					640
	nis	Asp	Pne	Pne	ьуs 645	ser	Ala	Met	Pro	G1u 650	GIY	Tyr	Val	Gln	Glu 655	Arg
45	Thr	Ile	Phe	Phe 660	Lys	Asp	Asp	Gly	Asn 665	Tyr	Lys	Thr	Arg	Ala 670	Glu	Val
	Lys	Phe	Glu 675	Gly	Asp	Thr	Leu	Val 680		Arg	Ile	Glu	Leu 685	Lys	Gly	Ile
	Asp	Phe 690	Lys	Glu	Asp	Gly	Asn 695		Leu	Gly	His	Lys 700		Glu	Tyr	Asn
50	Tyr 705	Asn	Ser	His	Asn			Ile	Met	Ala			Gln	Lys	Asn	_
		Lys	Val	Asn	Phe	710 Lys	Ile	Arg	His		715 Ile	Glu	Asp	Gly		720 Val
55	Gln	Leu	Ala	Asp 740		Tyr	Gln	Gln		730 Thr	Pro	Ile	Gly	Asp	735 Gly	Pro
,-•	Val	Leu	Leu		Asp	Asn	His	Tyr	745 Leu	Ser	Thr	Gln	Ser	750 Ala	Leu	Ser

			755					760					765					
	Lys	Asp 770	Pro	Asn (	Glu		Arg 775	qaA	His	Met	Val	Leu 780	Leu	Glu	Phe	Val		
5	Thr 785	Ala	Ala	Gly		Thr 790	Leu	Gly	Met	_	Glu 795	Leu	Tyr	Lys				
			(2)	INF	ORMA	TION	FOR	SEC	) ID	NO:7	8:							
10		(i	(A) (B) (C)	QUEN LENG TYPE STRA TOPO	TH: : nu NDED	3138 clei NESS	bas c ac : si	e pa id ngle	irs									
15				OLEC EATU		TYPE	: cD	AA										
20			(B)	NAM LOC OTH	ATIC	N: 1	3	135	equen	ce								
		()	(i) S	EQUE	NCE	DESC	RIPT	: NOI	SEC	OI O	NO: 7	8:						
25				TGG Trp													48	
30				GTG Val 20												_	96	
35				CAG Gln													144	
55				CAG Gln													192	
40				CTG Leu													240	
45				AAG Lys													288	
50				CGC Arg 100											His		336	
55				GAA Glu					Arg					Cys			384	
55	CCG	GCT	GGG	ATC	CTG	GTT	GAC	GCC	ATG	TCC	CAG	AAG	CAC	CTI	CAG	ATC	432	178

										179							
	Pro	Ala 130	Gly	Ile	Leu	Val	Asp 135	Ala	Met	Ser	Gln	Lys 140	His	Leu	Gln	Ile	
5															GAG Glu		480
10															CAG Gln 175		528
15															CAG Gln		576
															AAG Lys		624
20															CAG Gln		672
25															CTG Leu		720
30															TGG Trp 255		768
35															AGC Ser		816
33															TGG Trp		864
40															CTG Leu		912
45															ACC Thr		960
50											Thr				GAG Glu 335		1008
55					Val					Thr					Thr	GTA Val	1056
JJ	CGC	CTG	CTG	GTG	GGC	GGG	AAG	CTG	AAC	GTG	CAC	ATG	AAT	ccc	ccc	CAG	1104

										100								
	Arg	Leu	Leu 355	Val	Gly	Gly		Leu 360	Asn	Val	His	Met	Asn 365	Pro	Pro	Gln		
5						Ile							TCT Ser				1152	
10													CTG Leu				1200	
	TGC Cys	GTG Val	ATG Met	GAG Glu	TAC Tyr 405	CAC His	CAA Gln	GCC Ala	ACG Thr	GGC Gly 410	ACC Thr	CTC Leu	AGT Ser	GCC Ala	CAC His 415	TTC Phe	1248	
15	AGG Arg	AAC Asn	ATG Met	TCA Ser 420	CTG Leu	AAG Lys	AGG Arg	ATC Ile	AAG Lys 425	CGT Arg	GCT Ala	GAC Asp	CGG Arg	CGG Arg 430	GGT Gly	GCA Ala	1296	
20	GAG Glu	TCC Ser	GTG Val 435	ACA Thr	GAG Glu	GAG Glu	AAG Lys	TTC Phe 440	ACA Thr	GTC Val	CTG Leu	TTT Phe	GAG Glu 445	TCT Ser	CAG Gln	TTC Phe	1344	
25	AGT Ser	GTT Val 450	Gly	AGC Ser	AAT Asn	GAG Glu	CTT Leu 455	GTG Val	TTC Phe	CAG Gln	GTG Val	AAG Lys 460	ACT Thr	CTG Leu	TCC Ser	CTA Leu	1392	
30	CCT Pro 465	GTG Val	GTT Val	GTC Val	ATC Ile	GTC Val 470	CAC His	GGC Gly	AGC Ser	CAG Gln	GAC Asp 475	CAC	AAT Asn	GCC Ala	ACG Thr	GCT Ala 480	1440	
	ACT Thr	GTG Val	CTG Leu	TGG Trp	GAC Asp 485	AAT Asn	GCC Ala	TTT Phe	GCT Ala	GAG Glu 490	Pro	GGC	AGG Arg	GTG Val	CCA Pro 495	Phe	1488	
35	GCC Ala	GTC Val	CCI Pro	GAC Asp 500	Lys	GTG Val	CTG Leu	TGG Trp	CCG Pro	Gln	CTG Leu	TGT Cys	GAG Glu	GCG Ala 510	Leu	AAC Asn	1536	
40	ATG Met	AAA Lys	A TTC 5 Phe 519	Lys	GCC Ala	GAA Glu	GTG Val	CAG Gln 520	Ser	AAC Asr	CGG Arg	GGG Gly	C CTG y Leu 525	Thr	AAC Lys	GAG Glu	1584	
45	AAC Asr	CT( Lei 53(	ı Va:	TTC L Phe	CTC Lev	GCG Ala	CAC Glr 535	ı Lys	CTG Lev	TTC L Phe	AAC Ası	AAG ASI 54	n Ser	: AGC	: AGC	C CAC	1632	
50	CTC Lev 545	ı Gl	G GAO u Asj	С ТАО Э Туз	C AGT	GGC Gly 550	/ Let	G TCC	GTC Val	TCC l Se	TGC Trp 55!	, Se	C CAC	TTO	C AAG e Ası	a AGG n Arg 560	1680	
	GA( Gl:	AA As	C TT	G CCC	G GG( C Gl) 569	y Tr	AA Asi	C TAC	C ACC	TTO r Pho 57	e Tr	G CA p Gl	G TG( n Tr	TT	r GA e Asj 57	c GGG p Gly 5	1728	
55	GT	TA E	G GA	G GT	G TT	AA E	S AA	G CA	C CA	C AA	G CC	C CA	C TG	g aa	r ga	T GGG	1776	180

										101							
	Val	Met	Glu	Val 580	Leu	Lys	Lys	His	His 585	Lys	Pro	His	Trp	Asn 590	Asp	Gly	
	GCC	ATC	CTA	GGT	TTT	GTG	AAT	AAG	CAA	CAG	GCC	CAC	GAC	CTG	CTC	ATC	1824
5							Asn										
	AAC	AAG	CCC	GAC	GGG	ACC	TTC	TTG	TTG	CGC	TTT	AGT	GAC	TCA	GAA	ATC	1872
							Phe										
10		610					615					620					
							TGG										1920
	625	GIY	110	1111	116	630	Trp	цув	FIIE	Asp	635	PIO	Gru	Arg	ASII	640	
15																	
							ACC										1968
	Trp	Asn	Leu	Lys	Pro 645	Phe	Thr	Thr	Arg	Asp 650	Phe	Ser	Ile	Arg	Ser 655	Leu	
20	GCT	GAC	CGG	CTG	GGG	GAC	CTG	AGC	TAT	CTC	ATC	TAT	GTG	TTT	CCT	GAC	2016
	_						Leu										
				660					665					670			
	CGC	CCC	AAG	GAT	DAD	GTC	TTC	TCC	DAG	ጥልሮ	יים כי	ΔСТ	רכיזי	GTG	CTG	GCT	2064
25							Phe										2001
			675					680	_	-	-		685				
	***	CCTT	C TT TT	O A TI	cca	m a m	GTG		GG3	a. a	300		~~ <b>~</b>	ama	ama	aam.	2772
							Val										2112
30	•	690		<b>L</b>	-2	-3-	695	4				700					
	CAC	mmm	ama	2 2 00		mam	aan	~~ m	aam		~~~		. ~~	<b>a</b> aa		<b>ma</b> G	27.60
							GCA Ala										2160
	705					710			1114	O <sub>1</sub>	715	501	001			720	
35																	
							CCA										2208
	Met	Asp	Gin	Ala	Pro 725	Ser	Pro	Ala	Val		Pro	Gln	Ala	Pro		Asn	
					123					730					735		
40	ATG	TAC	CCA	CAG	AAC	CCT	GAC	CAT	GTA	CTC	GAT	CAG	GAT	GGA	GAA	TTC	2256
	Met	Tyr	Pro		Asn	Pro	Asp	His		Leu	qaA	Gln	Asp	-	Glu	Phe	
				740					745					750			
	GAC	CTG	GAT	GAG	ACC	ATG	GAT	GTG	GCC	AGG	CAC	GTG	GAG	GAA	CTC	TTA	2304
45							Asp										
			755					760					765				
	CGC	CGA	CCA	ATG	GAC	AGT	CTT	GAC	ሞሮሮ	CGC	СТС	TCG	ccc	CCT	GCC	GGT	2352
							Leu										2332
50	_	770			-		775	-		_		780				-	
	Cutur	ጥጥረ	n c c	ተርማ	GCC	מכא	CCC	TOO	CEC	TI CO	mar.	CIOTA N	000	000	000	ccc	2400
							GGC Gly										2400
	785					790	1				795			3		800	
55																	
	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	2448

										104								
	Asp	Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	Lys 810	Gly	Glu	Glu	Leu	Phe 815	Thr		
5					ATC Ile												2496	
10					TCC Ser												2544	
15					TTC Phe												2592	
					ACC Thr												2640	
20					ATG Met 885												2688	
25					CAG Gln												2736	
30					GCC Ala												2784	
35					AAG Lys											CTG Leu	2832	
33		His					Asn									ATG Met 960	2880	
40											Asn					CAC His	2928	
45					Gly					Ala					Gln	AAC Asn	2976	
50				: Gly					Leu					His		CTG Leu	3024	
			Glr					ъys					ı Lys			CAC His	3072	
55	TA	GT(	сто	CTC	GAC	TTC	C GTO	S ACC	C GCC	C GCC	GGG	TA E	C ACT	r cto	GG(	CATG	3120	182

183

1035

Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met

1030

GAC GAG CTG TAC AAG TAA 3138 5 Asp Glu Leu Tyr Lys 1045 (2) INFORMATION FOR SEQ ID NO:79: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1045 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single 15 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79: Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His 25 Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln Leu Leu Glu Gly Leu 30 Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln Val Gly Glu Asp Gly 75 Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys 85 90 Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg Cys Ile Arg His Ile 35 105 Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser 120 Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln Lys His Leu Gln Ile 135 140 40 Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr Gln Asp Thr Glu Asn 150 155 Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr Phe Ile Ile Gln Tyr 165 170 Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala Gln Leu Ala Gln Leu 45 185 Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala Leu Gln Gln Lys Gln 200 Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala Gln Thr Leu Gln Gln 215 220 50 Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys Thr Leu Gln Leu Leu 230 235 Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu Leu Ile Gln Trp Lys 245 250 Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro Pro Glu Gly Ser Leu 55 265 Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala Glu Ile Ile Trp Gln

			275					280					285			
	Asn	Arg 290	Gln	Gln	Ile	Arg	Arg 295	Ala	Glu	His	Leu	Cys 300	Gln	Gln	Leu	Pro
5	Ile 305	Pro	Gly	Pro	Val	Glu 310	Glu	Met	Leu	Ala	Glu 315	Val	Asn	Ala	Thr	Ile 320
	Thr	Asp	Ile	Ile	Ser 325	Ala	Leu	Val	Thr	Ser 330	Thr	Phe	Ile	Ile	Glu 335	Lys
	Gln	Pro	Pro	Gln 340	Val	Leu	Lys	Thr	Gln 345	Thr	Lys	Phe	Ala	Ala 350	Thr	Val
10	Arg	Leu	Leu 355	Val	Gly	Gly	Lys	Leu 360	Asn	Val	His	Met	Asn 365	Pro	Pro	Gln
	Val	Lys 370	Ala	Thr	Ile	Ile	Ser 375	Glu	Gln	Gln	Ala	Lys 380	Ser	Leu	Leu	Lys
15	Asn 385	Glu	Asn	Thr	Arg	Asn 390	Glu	Cys	Ser	Gly	Glu 395	Ile	Leu	Asn	Asn	Cys 400
	Cys	Val	Met	Glu	Tyr 405	His	Gln	Ala	Thr	Gly 410	Thr	Leu	Ser	Ala	His 415	Phe
				420			_		425	Arg		_		430		
20			435					440		Val			445			
		450					455			Gln		460				
25	465					470				Gln	475					480
				-	485					Glu 490		_			495	
				500	_				505	Gln				510		
30			515					520		Asn			525			
		530					535	-		Phe		540				
35	545					550				Ser	555					560
					565			_		Phe 570					575	
40				580					585					590		
40			595					600		Gln			605			
		610					615			Arg		620				
45	625	_				630		_		Asp	635					640
	_				645					Asp 650					655	
				660					665					670		
50			675					680		Tyr			685	;		
		690	)				695	;		Gln		700	)			
55	705	,				710	)			Gly	715	;				720
	⋈⇔⊷	000	1217		U ~~	Y	222	3 017	1/2/	[ '370	, pr	, (÷17		, pro	1777	T

185

					725					730					735		
	Met	Tyr	Pro	Gln 740	Asn	Pro	Asp	His	Val 745	Leu	Asp	Gln	Asp	Gly 750	Glu	Phe	
5	Asp	Leu	Asp 755	Glu	Thr	Met	Asp	Val 760		Arg	His	Val	Glu 765		Leu	Leu	
	Arg	Arg 770		Met	Asp	Ser	Leu 775		Ser	Arg	Leu	Ser 780		Pro	Ala	Gly	
	Leu 785	Phe	Thr	Ser	Ala	Arg 790	Gly	Ser	Leu	Ser	Trp 795		Pro	Arg	Ala		
10		Pro	Pro	Val	Ala		Met	Val	Ser	Lys		Glu	Glu	Leu	Phe	800 Thr	
	Gly	Val	Val	Pro	805 Ile	Leu	Val	Glu		810 Asp	Gly	Asp	Val		815 Gly	His	
	Lys	Phe		820 Val	Ser	Gly	Glu	_	825 Glu	Gly	Asp	Ala		830 Tyr	Gly	Lys	
15	Leu		835 Leu	Lys	Phe	Ile		840 Thr	Thr	Gly	Lys		845 Pro	Val	Pro	Trp	
	Pro	850 Thr	Leu	Val	Thr	Thr	855 Leu	Thr	Tyr	Gly	Val	860 Gln	Cys	Phe	Ser	Arg	
	865					870					875					880	
20	Tyr	Pro	Asp	His	Met 885	Lys	Gln	His	Asp	Phe 890	Phe	Lys	Ser	Ala	Met 895	Pro	
	Glu	Gly	Tyr	Val 900	Gln	Glu	Arg	Thr	Ile 905	Phe	Phe	Lys	Asp	Asp 910	Gly	Asn	
25	Tyr	Lys	Thr 915	Arg	Ala	Glu	Val	Lys 920	Phe	Glu	Gly	Asp	Thr 925	Leu	Val	Asn	
	Arg	Ile 930	Glu	Leu	Lys	Gly	Ile 935	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	
	Gly 945	His	Lys	Leu	Glu	Tyr 950		Tyr	Asn	Ser	His 955		Val	Tyr	Ile	Met 960	
30	_	Asp	Lys	Gln	Lys 965		Gly	Ile	Lys			Phe	Lys	Ile	_		
	Asn	Ile	Glu	Asp		Ser	Val	Gln		970 Ala	Asp	His	Tyr		975 Gln	Asn	
35	Thr	Pro		980 Gly	Asp	Gly			985 Leu	Leu	Pro			990 His	Tyr	Leu	
30	Ser	Thr	995 Gln	Ser	Δla	T.e.u		1000	λαη	Dro	λαη		1005	λrα	λαρ	uie	
		1010	0111	501	ALU		1015	цуз	rsb	FIO		1020	цуз	ALG	ASP	1113	
		Val	Leu	Leu			Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu			
40	025 Asp	Glu	Leu	Tyr	Lys	1030				:	1035					1040	
			(0)		1045												
			(2)	) IN	FORM	ATIO	N FO.	R SE	Q ID	NO:	80:						
45		(		EQUEI LENC													
				TYPI					LO								
			(C)	STR	ANDE	DNES.	S: s	ingl	е								
50			(D)	TOP	orog.	Y: 1	inea	r									
		(:	xi) :	SEQUI	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	80:					
	TGG	GATC	CTC 2	AGGC	CGTG	CT G	CTGG	CCG									28
55			(2	) IN	FORM	ATIO:	N FO	R SE	Q ID	NO:	81:						

5	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:	0.7
	(2) INFORMATION FOR SEQ ID NO:82:	27
15	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
20	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:	
25	TGGGATCCGA GAAGTCTATA TCCCATC	27
23	(2) INFORMATION FOR SEQ ID NO:83:	
30	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 28 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:	
	TGGGATCCTT AGAAGTCTAT ATCCCATC	28
40	(2) INFORMATION FOR SEQ ID NO:84: (i) SEQUENCE CHARACTERISTICS:	
45	<ul><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:	
50	GTCTCGAGCC ATGAACGCCC CCGAGCGG	28
	(2) INFORMATION FOR SEQ ID NO:85:	
55	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 30 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
		186

	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:	
	GTGAATTCTC GTCTGATTTC TGGCAGGAGG	30,
10	(2) INFORMATION FOR SEQ ID NO:86:	
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid	
15	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>	•
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:	
20	GTGAATTCTT TACGTCTGAT TTCTGGCAGG	30
	(2) INFORMATION FOR SEQ ID NO:87:	
25	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
30		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:	
	GTCTCGAGCC ATGGACGAAC TGTTCCCCCT CATC	34
35	(2) INFORMATION FOR SEQ ID NO:88:	
	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
40	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:	
	GTGGATCCAA GGAGCTGATC TGACTCAGCA G	31
	(2) INFORMATION FOR SEQ ID NO:89:	
50	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 32 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
55	(D) TOPOLOGY: linear	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:	
	GTGGATCCTT AGGAGCTGAT CTGACTCAGC AG	32
5	(2) INFORMATION FOR SEQ ID NO:90:	
10	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 32 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:	
10	CCTCCTAAGC TTATCATGGA CCATTATGAT TC	32
	(2) INFORMATION FOR SEQ ID NO:91:	
20	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs	
	(A) BENGIN: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
25	(b) TOPOLOGI: Tilleat	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:	
30	CCTCCTGGAT CCCTGCGCAG GATGATGGTC CAG	33
30	(2) INFORMATION FOR SEQ ID NO:92:	
35	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 45 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:	
	GGATGGAAGC TTCAATGGCT GCCATCCGGA AGAAACTGGT GATTG	45
45	(2) INFORMATION FOR SEQ ID NO:93:	
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 45 base pairs  (B) TYPE: nucleic acid	
50	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:	
55	GGATGGGGAT CCTCACAAGA CAAGGCAACC AGATTTTTC TTCCC	45

	(2) INFORMATION FOR SEQ ID NO:94:	
5	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 29 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:	
	GGGAAGCTTC CATGAGCGAG ACGGTCATC	Ż9
15	(2) INFORMATION FOR SEQ ID NO:95:  (i) SEQUENCE CHARACTERISTICS:	
	<ul><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
20	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:	
25	CCCGGATCCT CAGGGAGAAC CCCGCTTC	28
	(2) INFORMATION FOR SEQ ID NO:96:	
30	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 30 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:	
	GTGAATTCGA CCATGGAGCG GCCCCCGGGG	30
40	(2) INFORMATION FOR SEQ ID NO:97:	
	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li></ul>	
45	<ul><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:	
	GTGGTACCCA TTCTGTTAAC CAACTCC	27
	(2) INFORMATION FOR SEQ ID NO:98:	
55	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li></ul>	
		189

	190	
	<ul><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:	
	GTGGTACCTC ATTCTGTTAA CCAACTCC	28
10	(2) INFORMATION FOR SEQ ID NO:99:	
15	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:	
20	GTCTCGAGAG ATGCTGTCCC GTGGGTGG	28
	(2) INFORMATION FOR SEQ ID NO:100:	
25	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
30	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:	
35	GTGAATTCGC TTCCTCTTGA GGGAACC	27
33	(2) INFORMATION FOR SEQ ID NO:101:	
40	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:	
,,,	GTGAATTCAC TTCCTCTTGA GGGAACC	27
	(2) INFORMATION FOR SEQ ID NO:102:	
50		
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid	
55	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	

. 191

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:	
_	GTCTCGAGCC ATGGAGAACT TCCAAAAGG	29
5	(2) INFORMATION FOR SEQ ID NO:103:	
10	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:	
	GTGGATCCCA GAGTCGAAGA TGGGGTAC	28
20	(2) INFORMATION FOR SEQ ID NO:104:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs	
	(B) TYPE: nucleic acid	
25	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:	
30	GTGGATCCTC AGAGTCGAAG ATGGGGTAC	29
	(2) INFORMATION FOR SEQ ID NO:105:	
25	(i) SEQUENCE CHARACTERISTICS:	
35	(A) LENGTH: 30 base pairs (B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
40		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:	
	GTGAATTCGG CGATGCCAGA CCCCGCGGCG	30
45	(2) INFORMATION FOR SEQ ID NO:106:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs	
	(B) TYPE: nucleic acid	
50	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:	
55		
	GTGGATCCCA GGCACAGGCA GCCTCAGCCT TC	32 191

			(2)	INF	ORMA	TION	FOR	SEQ	ID	NO:1	07:							
5		(i	(A) (B) (C)	LENG TYPE STRA	TH: : nu NDED	33 b clei NESS	CTER ase c ac : si near	pair id ngle	S									
10		(x	i) S	EQUE	NCE	DESC	RIPT	: NOI	SEQ	ID	NO:1	07:						
	GTGG.	ATCC	TC A	.GGCA	CAGG	C AG	CCTC	AGCC	TTC								33	
15		<ul> <li>(2) INFORMATION FOR SEQ ID NO:108:</li> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 2616 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> </ul>																
20		(A) LENGTH: 2616 base pairs (B) TYPE: nucleic acid																
25	(A) LENGTH: 2616 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA  (ix) FEATURE:  (A) NAME/KEY: Coding Sequence  (B) LOCATION: 12613  (D) OTHER INFORMATION:  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:  ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG  48																	
		(D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA  (ix) FEATURE:  (A) NAME/KEY: Coding Sequence  (B) LOCATION: 12613																
00																		
30		(х	1) 5	EQUE	ENCE	DESC	RIPI	CTON:	SEÇ	) ID	NO:1	.08:						
35																	48	
		-															96	
40																	144	
45																	192	
50																	240	
55																	288	
ວວ	CGC	(2) INFORMATION FOR SEQ ID NO:108:  (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2616 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence (B) LOCATION: 12613 (D) OTHER INFORMATION:  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:  THE GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG (A) CTG GTG AGC AGG GGG GTG GTG CCC ATC CTG (B) Leu Phe Thr Gly Val Val Pro lle Leu (B) Location: 10 15  THE GTG AGC AGG GGC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC (C) CTG GAG CTG GAC GGC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC (C) CTG GAG GGC GAT GCC ACC TAC GGC AAG TTC AGC GTG TCC GGC (C) CTG GAC GGC GAT GCC ACC TAC GGC AAG TTC ACC CTG AAG TTC ATC (C) CTG GGC GAG GGC GAT GCC CTG CCC GGC CACC CTC GTG ACC ACC (C) CTG ACC ACC GGC AAG CTG CCC TGG CCC ACC CTC GTG ACC ACC (C) CTG ACC ACC GGC AAG CTC TAC GGC CACC ACC CTC GTG ACC ACC (C) THE THRE COUNTY TO THE LEU VAL THRE THRE (C) CTG ACC ACC GGC GTG CAC TGC CCC TGC CCC GAC CAC ATG AAG (C) CTG ACC TAC GGC GTG CAC TTC AGC CGC TAC CCC GAC CAC ATG AAG (C) CTG ACC TAC GGC GTG CAC TTC AGC CGC TAC CCC GAC CAC ATG AAG (C) CTG ACC TAC GGC GTG CAC TTC AGC CGC TAC CCC GAC CAC ATG AAG (C) CTG ACC TAC GGC GTG CAC TTC AGC CGC TAC CCC GAC CAC ATG AAG (C) CTG ACC TAC GGC GTG CAC TTC TCC AAG TCC GCC AGC CAC ATG AAG (C) CTG ACC TCC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG (C) CTG ACC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG (C) CTG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG (C) CTG CAC GAC CTC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG (C) CTG CAC GAC CTC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG (C) CTG CAC GAC CTC TTC TTC AAG TCC GCC CTG CAC CTC CTG CAG GAG (C) CTG CAC GAC CTC TTC TTC CAC GCC CTG CCC GAA GGC TAC GTC CAG GAG (C) CTG CAC GAC TTC TTC CAG CCC GCC CTG CCC GAA GGC TAC GTC CAG GAG (C) CTG CAC GAC CTC TTC TTC AAG TCC GCC CTG CCC GAA GGC TAC GTC CAG GAG (C) CTG CAC GAC CTC TTC TTC AAG TCC GCC CTG CCC GAA GGC TAC GTC CAG GAG (C) CTG CA													336	192		

									•	193		-					
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
5			TTC Phe 115														384
10			TTC Phe														432
15			AAC Asn														480
, ,			AAG Lys														528
20			CTC Leu														576
25			CTG Leu 195														624
30			GAC Asp														672
35			GCC Ala														720
00			AGA Arg														768
40			CAC His														816
45			CAC His 275														864
50			TGC Cys														912
55			CGC Arg														960
55	TAC	GCC	ATT	GCC	GGC	GGC	AAA	GCG	CAC	TGT	GGA	CCG	GCA	GAG	CTC	TGC	1008

									1	107								
	Tyr	Ala	Ile	Ala	Gly 325	Gly	Lys	Ala	His	Cys 330	Gly	Pro	Ala	Glu	Leu 335	Cys		
5	GAG Glu	TTC Phe	TAC Tyr	TCG Ser 340	CGC Arg	GAC Asp	CCC Pro	GAC Asp	GGG Gly 345	CTG Leu	CCC Pro	TGC Cys	AAC Asn	CTG Leu 350	CGC Arg	AAG Lys	1056	
10	CCG Pro	TGC Cys	AAC Asn 355	CGG Arg	CCG Pro	TCG Ser	GGC Gly	CTC Leu 360	GAG Glu	CCG Pro	CAG Gln	CCG Pro	GGG Gly 365	GTC Val	TTC Phe	GAC Asp	1104	
													CAG Gln				1152	
15	CTG Leu 385	GAG Glu	GGC Gly	GAG Glu	GCC Ala	CTG Leu 390	GAG Glu	CAG Gln	GCC Ala	ATC Ile	ATC Ile 395	AGC Ser	CAG Gln	GCC Ala	CCG Pro	CAG Gln 400	1200	
20	GTG Val	GAG Glu	AAG Lys	CTC Leu	ATT Ile 405	GCT Ala	ACG Thr	ACG Thr	GCC Ala	CAC His 410	GAG Glu	CGG Arg	ATG Met	CCC Pro	TGG Trp 415	TAC Tyr	1248	
25	CAC His	AGC Ser	AGC Ser	CTG Leu 420	ACG Thr	CGT Arg	GAG Glu	GAG Glu	GCC Ala 425	GAG Glu	CGC Arg	AAA Lys	CTT	TAC Tyr 430	TCT Ser	GGG Gly	1296	
30	GCG Ala	CAG Gln	ACC Thr 435	Asp	GGC Gly	AAG Lys	TTC Phe	CTG Leu 440	Leu	AGG Arg	CCG Pro	CGG Arg	AAG Lys 445	GAG Glu	CAG Gln	GGC	1344	
	ACA Thr	TAC Tyr 450	Ala	CTG Leu	TCC Ser	CTC Leu	ATC Ile 455	Tyr	GGG	AAG Lys	ACG Thr	GTG Val 460	туг	CAC His	TAC	CTC Leu	1392	
35	ATC Ile 465	Sei	CAA	GAC Asp	AAG Lys	GCG Ala	Gly	AAG Lys	TAC Tyr	TGC Cys	ATT Ile 475	Pro	GAG Glu	GGC Gly	ACC Thr	AAG Lys 480	1440	
40	TTI Phe	GA(	C ACC	G CTC	TGG Trp	Glr	CTC	GTG Val	GAC	TAT Tyr 490	Lev	AAC Lys	G CTC	AAG Lys	GC0 Ala 495	GAC Asp	1488	
45	GGG Gly	G CTO	C ATO	TAC Tyr 500	Суя	C CTO	AAC 1 Lys	G GAG	GC0 1 Ala 509	a Cys	CCC F Pro	AA(	C AGO	C AGT Ser	Ala	C AGC a Ser	1536	
50	AA( Asr	C GC n Al	C TC a Se 51	r Gly	GC Ala	r GC a Ala	r GC	CCC Pro	o Th	A CTO	C CCA	A GCO	C CA( a Hi: 52!	s Pro	A TC	C ACG r Thr	1584	
	TT( Le	G AC u Th 53	r Hi	T CCT	r CAG	G AG	A CG g Ar 53	g Il	C GA	C AC	C CTO	C AA u As 54	n Se	A GA' r As	r GG p Gl	A TAC y Tyr	1632	
55	AC	c cc	T GA	G CC	A GC	A CG	C AT	A AC	G TC	c cc	A GA	C AA	A CC	G CG	g cc	G ATG	; 1680	194

										.00							
	Thr 545	Pro	Glu	Pro	Ala	Arg 550	Ile	Thr	Ser	Pro	Asp 555	Lys	Pro	Arg	Pro	Met 560	
5												AGC Ser					1728
10												AAC Asn					1776
15												GTG Val					1824
.0												ATC Ile 620					1872
20												ATG Met					1920
25												CGG Arg					1968
30												ATG Met					2016
35												GAG Glu					2064
												GGG Gly 700					2112
40												GCC Ala					2160
45												TTT Phe					2208
50												CGC Arg					2256
55												AAC Asn					2304
<b></b>	TCC	AGC	CGC	AGC	GAT	GTC	TGG	AGC	TAT	GGG	GTC	ACC	ATG	TGG	GAG	GCC	2352

PCT/DK98/00145 WO 98/45704

									-	196						•	
	Ser	Ser 770	Arg	Ser	Asp	Val	Trp 775	Ser	Tyr	Gly	Val	Thr 780	Met	Trp	Glu	Ala	
5				GGC Gly												_	2400
10				ATC Ile													2448
				CTG Leu 820													2496
15				CCC Pro													2544
20				CTG Leu													2592
25				GCT Ala				TGA									2616
30		(:	i) S	) IN EQUE LEN	NCE (	CHAR.	ACTE	RIST	ICS:		109:						
35			(C) (D)	TYP. STR. TOP	ANDE: OLOG	ONES Y: 1	S: s inea	ingl r									
40		(-	v) F	MOLE RAGM SEQU	ENT	TYPE	: in	tern	al	מד חי	NO.	109.					
										Thr				Pro		: Leu	
45	1 Val	Glu	Leu	Asp	5 Gly	Asp	Val	Asn	. Gly 25	10 His	Lys	Phe	Ser	Val	15 Ser	Gly	
10			35	Gly	_			40	Gly	_			45	Lys		· Ile	
50	_	50			_		55			_		60				Thr Lys	
	65 Gln	His	Asp	Phe	Phe	70 Lys	Ser	Ala	. Met	Pro 90	75 Glu	ı Gly	туг	. Val	l Glr 95	80 n Glu	
55	Arg	Thr	Ile	Phe	Phe	Lys	Asp	) Asp	Gly 105	/ Asi	тул	r Lys	Thi	2 Arg	g Ala	a Glu	
	Val	. Lys	Phe	Glu	ı Gly	Asp	Thi	Leu	ı Val	l Ası	ı Arg	ı Ile	e Glu	ı Let	ı Ly:	s Gly	4.

			115					120					125			
		130			Glu		135	Asn	Ile			140	Lys			_
5	145				His	150					155					160
					Asn 165					170					175	
				180					185					190		
10			195		Pro			200					205			
		210			Asn		215					220				
15	225				Gly	230					235					240
					Arg 245					250					255	
				260	Pro				265					270		
20			275		Lys			280					285			
		290			Arg		295					300				
25	305				His	310					315					320
					Gly 325					330					335	
••				340	Arg				345					350		
30			355		Pro			360					365			
		370			Ala		375					380				
35	385				Ala	390					395					400
					Ile 405					410					415	
				420	Thr				425					430		
40			435		Gly			440					445			
		450			Ser		455					460				
45	465				Lys	470					475					480
					Trp 485					490					495	Asp
				500	Cys				505					510		
50			515		Ala			520					525			
		530			Gln		535					540	Ser			
55	545				Ala	550					555					560
	Pro	Met	Asp	Thr	Ser	Val	Tvr	Glu	Ser	Dro	ጥነረም	Car	λer	Dro	C1	<b>~1</b>

198

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570
                      565
      Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn Leu Leu Ile Ala
                                     585
                  580
      Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg Gln Gly Val
5
                                 600
                                                      605
      Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile Lys Val Leu Lys
                             615
                                                  620
      Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met Arg Glu Ala Gln
                          630
10
      Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg Leu Ile Gly Val
                                          650
      Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met Ala Gly Gly Gly
                  660
                                     665
      Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu Ile Pro Val Ser
15
                                 680
      Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly Met Lys Tyr Leu
                              695
                                                  700
      Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn Val Leu
                          710
                                              715
20
      Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys
                      725
                                          730
      Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg Ser Ala Gly Lys
                                      745
      Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn Phe Arg Lys Phe
25
                                  760
      Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr Met Trp Glu Ala
                              775
      Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys Gly Pro Glu Val
                          790
                                              795
30
      Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys Pro Pro Glu Cys
                                          810
      Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp Ile Tyr Lys Trp
                                     825
      Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg Ala Cys
35
                               840
      Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro Gly Ser Thr Gln
                              855
      Lys Ala Glu Ala Ala Cys Ala
                          870
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                (2) INFORMATION FOR SEQ ID NO:110:
             (i) SEQUENCE CHARACTERISTICS:
               (A) LENGTH: 2598 base pairs
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               (B) TYPE: nucleic acid
               (C) STRANDEDNESS: single
               (D) TOPOLOGY: linear
             (ii) MOLECULE TYPE: cDNA
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             (ix) FEATURE:
                (A) NAME/KEY: Coding Sequence
                (B) LOCATION: 1...2595
                (D) OTHER INFORMATION:
55
             (xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:
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199

5												TAC Tyr					48
J												GGC Gly					96
10												GGC Gly					144
15			_	_		_			_		_	CCC Pro 60	_	_		_	192
20	Leu 65	Asn	Gly	Thr	Tyr	Ala 70	Ile	Ala	Gly	Gly	Lys 75	GCG Ala	His	Cys	Gly	Pro 80	240
25												GAC Asp					288
												CTC					336
30		_										CGT Arg					384
35												CAG Gln 140					432
40												ACG Thr					480
45												GAG Glu					528
												CTG Leu					576
50												TAT Tyr					624
55												AAG Lys 220					672

PCT/DK98/00145

WO 98/45704

5	GGC Gly													720
Ü	AAG Lys													768
10	 AGT Ser	 											_	816
15	CCA Pro													864
20	GAT Asp 290													912
25	CGG Arg													960
	ĊCA Pro													1008
30	CTC Leu													1056
35	CAG Gln													1104
40	GTG Val 370									Glu				1152
45	 GAG Glu								Pro					1200
40	ATT			Gln				Met						1248
50			Pro				Leu					Glı	G GAG	1296
55		Ser				ı Lev					Ser		GGG Gly	1344

5	ATG Met	AAG Lys 450	TAC Tyr	CTG Leu	GAG Glu	GAG Glu	AAG Lys 455	AAC Asn	TTT Phe	GTG Val	CAC His	CGT Arg 460	GAC Asp	CTG Leu	GCG Ala	GCC Ala	1392
				CTG Leu													1440
10				AAA Lys													1488
15				AAG Lys 500													1536
20				TTC Phe													1584
25	ATG Met	TGG Trp 530	GAG Glu	GCC Ala	TTG Leu	TCC Ser	TAC Tyr 535	GGC Gly	CAG Gln	AAG Lys	CCC Pro	TAC Tyr 540	AAG Lys	AAG Lys	ATG Met	AAA Lys	1632
	GGG Gly 545	CCG Pro	GAG Glu	GTC Val	ATG Met	GCC Ala 550	TTC Phe	ATC Ile	GAG Glu	CAG Gln	GGC Gly 555	AAG Lys	CGG Arg	ATG Met	GAG Glu	TGC Cys 560	1680
30				TGT Cys													1728
35				TGG Trp 580													1776
40				TGT Cys													1824
45	GGC Gly	AGC Ser 610	ACA Thr	CAG Gln	AAG Lys	GCT Ala	GAG Glu 615	GCT Ala	GCC Ala	TGT Cys	GCC Ala	TGG Trp 620	GAT Asp	CCA Pro	CCG Pro	GTC Val	1872
				GTG Val													1920
50				GAG Glu													1968
55	TCC Ser	GGC Gly	GAG Glu	GGC Gly 660	GAG Glu	GGC Gly	GAT Asp	GCC Ala	ACC Thr 665	TAC Tyr	GGC Gly	AAG Lys	CTG Leu	ACC Thr 670	CTG Leu	AAG Lys	2016

202

5	_	_		_	_	_			_		CCC Pro 685	_		_	2064
Ü											TAC Tyr				2112
10										_	GAA Glu				2160
15											TAC Tyr				2208
20											CGC Arg				2256
25											GGG Gly 765				2304
											GCC Ala				2352
30											AAC Asn				2400
35	_			_		_					_		_	GGC Gly	2448
40		_		_	Leu				His			_	Gln	TCC Ser	2496
45				Lys				Lys				Val		CTG Leu	2544
			Val				Ile				Asp			TAC Tyr	2592
50	AAG Lys 865														2598

55 (2) INFORMATION FOR SEQ ID NO:111:

203

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(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 865 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
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(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

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      Arg Ala Glu Ala Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly
15
                  20
      Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu
                                  40
      Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln
20
      Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro
                          70
                                              75
      Ala Glu Leu Cys Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys
      Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro
25
                                      105
      Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg
                                  120
      Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser
                              135
                                                  140
30
      Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg
                          150
                                              155
      Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys
                      165
                                          170
      Leu Tyr Ser Gly Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg
35
                                      185
      Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val
                                  200
      Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro
                              215
                                                  220
40
      Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys
                          230
                                              235
      Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn
                                          250
      Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala
45
                  260
                                      265
      His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn
                                  280
                                                      285
      Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys
                              295
                                                  300
50
      Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser
                          310
                                              315
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55
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203

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				Val	405					410					415	
				Gly 420					425					430		
10			435	Ser				440					445			
		450		Leu			455					460				
15	465			Leu		470					475					480
	-			Lys Lys	485					490					495	
20				500 Phe					505					510		
20			515	Ala				520					525			
		530		Val			535					540				
25	545			Cys		550					555					560
				Trp	565					570					575	
30		-		580 Cys					585					590		
	Gly	Ser	595 Thr	Gln	Lys	Ala	Glu	600 Ala		Cys	Ala	Trp	605 Asp		Pro	Val
	Ala	610 Thr		Val	Ser	Lys	615 Gly		Glu	Leu			Gly	. Val	Va1	
35	625 Ile	Leu	Val	Glu			Gly	Asp	Val				Lys	Phe		
	Ser	Gly	Glu				Asp	Ala				Lys	Leu	Thr 670		Lys
40	Phe	Ile				Gly	Lys	Leu 680			Pro	Trp	Pro 685	Thr		ı Val
	Thr	Thr			туг	Gly	Val	Gln		Phe	Ser	Arg	туг		Ası	His
45	Met 705	Lys		ı His	Asp	Phe 710	Ph∈		Ser	Ala	Met 715	Pro		ı Gly	ту:	r Val 720
			Arg	Thr	1le 725	Phe		e Lys	a Asp	Asp 730		/ Asr	туз	r Lys	Th:	r Arg 5
	Ala	Glu	ı Val	L Lys 740		Glu	Gly	/ Asp	745		ı Val	Asr	n Arg	g Ile 75		u Leu
50	_		755	5				760	)				76	5		s Leu
		770	)				779	5				780	)			s Gln
55	785	5				790	)				79	5				u Asp 800
	Gly	y Set	r Va	l Glr	ı Leı	Ala د	a As	p His	з Ту	r Gl	n Gl	n Ası	n Th	r Pr	o Il	e Gly

										205								
					805					810					815			
	Asp	Gly	Pro		Leu	Leu	Pro	Asp		His	Tyr	Leu	Ser		Gln	Ser		
	אן א	T 011	Co~	820	N a m	Dro	Nan	C1.,	825	7 ~~~	7.55	uia	Mot	830	Lou	Lon		
5	Ala	Leu	835	гуя	Asp	PIO	ASII	840	гуз	Arg	Asp	піз	Met 845	vaı	ьеи	ьeu		
Ū	Glu	Phe		Thr	Ala	Ala	Gly		Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr		
		850					855				-	860	_					
	Lys													•				
10	865																	
10			(2)	INF	ORMA	TION	FOF	SEC	) ID	NO:	12:							
			•-•					_										
		( i	-	_		CHARA												
15						1635		-	irs									
13						nclei ONESS			•									
						: li			_									
20						TYPE	: cI	ONA										
20		( 3	ix) I	EAT	JRE:													
			(A)	NAM	1E/KE	EY: C	Codir	ng Se	eque	ıce								
						ON: 1												
25			(D)	OTI	HER ]	INFOR	TAM	ION:										
25		()	(i) 9	EOUE	ENCE	DESC	RIP	TON:	: SE	o ID	NO:	112:						
		(-	, -							2								
													GGC				48	
30		Glu	Asn	Phe	Gln 5	Lys	Val	Glu	Lys		Gly	Glu	Gly	Thr	_	Gly		
30	1				5					10					15			
	GTT	GTG	TAC	AAA	GCC	AGA	AAC	AAG	TTG	ACG	GGA	GAG	GTG	GTG	GCG	CTT	96	
	Val	Val	Tyr	-	Ala	Arg	Asn	Lys	Leu	Thr	Gly	Glu	Val		Ala	Leu		
35				20					25					30				
33	AAG	AAA	ATC	CGC	CTG	GAC	ACT	GAG	ACT	GAG	GGT	GTG	ccc	AGT	ACT	GCC	144	
	Lys	Lys	Ile	Arg	Leu	Asp	Thr	Glu	Thr	Glu	Gly	Val	Pro	Ser	Thr	Ala		
			35					40					45					
40	አጥሮ	CGA	CAG	እጥሮ	ጥርጥ	CTC	CTT	אאכ	CNC	Cathar	אאר	CNT	CCT	ידיתית	አ ጥጥ	CTC	192	
40													Pro				1,92	
		50					55	•	-			60						
																		·
45													TAC Tyr				240	
40	65	Бец	пец	ден	vai	70	1115	1111	GIG	ASII	75	цец	TYL	пси	Val	80		
													GCC				288	
50	GIu	Phe	Leu	His	GIn 85	Asp	Leu	Lys	Lys	Phe 90	Met	Asp	Ala	Ser	A1a 95	Leu		
50					0.5					90					,,			
	ACT	GGC	ATT	CCT	CTT	CCC	CTC	ATC	AAG	AGC	TAT	CTG	TTC	CAG	CTG	CTC	336	
	Thr	Gly	Ile		Leu	Pro	Leu	Ile	_	Ser	Tyr	Leu	Phe		Leu	Leu		
55		,		100					105					110				
00	CAG	GGC	CTA	GCT	TTC	TGC	CAT	TCT	CAT	CGG	GTC	CTC	CAC	CGA	GAC	CTT	384	
								- <del>-</del>	<b>-</b>									205

										206								
	Gln	Gly	Leu 115	Ala	Phe	Cys	His	Ser 120	His	Arg	Val	Leu	His 125	Arg	Asp	Leu		
5						CTT Leu	_				_	_	_				432	
10						AGA Arg 150	_	_		_		_		_			480	
15						CTG Leu										_	528	
13						ACA Thr											576	
20						ACT Thr										_	624	
25						CGG Arg										_	672	
30						GTT Val 230										_	720	
35						CAA Gln											768	
33						TTG Leu											816	
40						AAG Lys											864	
45			Lys			CCC Pro		Leu					Pro				912	
50		Met				GGC Gly 310						Gly					960	
55						GGC					His				_	Ser	1008	
55	GGC	GAC	GGC	: GAG	GGC	GAT	' GCC	: ACC	TAC	: GGC	AAG	CTG	ACC	CTG	AAC	TTC	1056	206

207

										207								
	Gly	Glu	Gly	Glu 340	Gly	Asp	Ala	Thr	Tyr 345	Gly	Lys	Leu	Thr	Leu 350	Lys	Phe		
5					GGC Gly													1104
10					GGC Gly													1152
15					TTC Phe													1200
10					TTC Phe 405													1248
20					GAG Glu													1296
25	_				AAG Lys													1344
30					AGC Ser													1392
25					GTG Val													1440
35					GCC Ala 485													1488
40					CTG Leu													1536
45					CCC Pro													1584
50					GCC Ala								Glu			AAG Lys	т	1633
	AA																	1635
			12	) The	FORM	מייים.	NT EO	79 G	0 TD	NO.	112.							

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

207

208

(A) LENGTH: 544 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

10		(2	K1) S	EQUI	SNCE	DESC	CRIP	rion:	SEÇ	DID	NO:	113:				
10	Mot	Glu	Λen	Dhe	GI n	Larg	<b>37 - 1</b>	C1	Tara	710	<i>α</i> 1	<b>a</b> 1	<b>~</b> 1	mh	Ma esse	Gly
	1				5					10			_		15	_
	Val	Val	Tyr	Lys 20	Ala	Arg	Asn	Lys	Leu 25	Thr	Gly	Glu	Val	Val 30	Ala	Leu
15	Lys	Lys	Ile 35	Arg	Leu	Asp	Thr	Glu 40	Thr	Glu	Gly	Val	Pro 45	Ser	Thr	Ala
	Ile	Arg 50	Glu	Ile	Ser	Leu	Leu 55	Lys	Glu	Leu	Asn	His 60		Asn	Ile	Val
	Lvs		Len	Δen	Va 1	Tle		Thr	Glu	yen	Larc	Leu	Ф. с.	Ton	17a T	Dho
20	65					70					75					80
					85					90		Asp			95	
	Thr	Gly	Ile	Pro 100	Leu	Pro	Leu	Ile	Lys 105	Ser	Tyr	Leu	Phe	Gln 110	Leu	Leu
25	Gln	Gly	Leu 115	Ala	Phe	Cys	His	Ser 120	His	Arg	Val	Leu	His 125	Arg	Asp	Leu
	Lvs	Pro		Asn	Leu	Leu	Ile		Thr	Glu	Glv	Ala		Lvs	Len	Ala
		130					135					140				
30	145	PHE	СТУ	Leu	Ala	150	Ald	Pne	GIĀ	vai	155	vaı	Arg	Thr	ıyr	Thr 160
		Glu	Val	Val	Thr		Trp	Tvr	Ara	Δla		Glu	Tle	Leu	Len	
					165					170					175	
				180					185			Ser		190		
35	Phe	Ala	Glu 195	Met	Val	Thr	Arg	Arg 200	Ala	Leu	Phe	Pro	Gly 205	Asp	Ser	Glu
	Ile	Asp 210	Gln	Leu	Phe	Arg	Ile 215	Phe	Arg	Thr	Leu	Gly 220	Thr	Pro	Asp	Glu
	Val	Val	Trp	Pro	Gly	Val	Thr	Ser	Met	Pro	Asp		Lvs	Pro	Ser	Phe
40	225		_		-	230					235	. 4				240
	Pro	Lys	Trp	Ala	Arg 245	Gln	qaA	Phe	Ser	Lys 250	Val	Val	Pro	Pro	Leu 255	Asp
	Glu	Asp	Gly	Arg 260	Ser	Leu	Leu	Ser	Gln 265	Met	Leu	His	Tyr	Asp 270		Asn
45	Lys	Arg	Ile 275		Ala	Lys	Ala	Ala 280		Ala	His	Pro	Phe 285		Gln	Asp
	Val	Thr 290		Pro	Val	Pro	His 295		Arg	Leu	Trp	Asp		Pro	Val	Ala
	Thr		Val	Ser	Larg	Glv		Glu	T.a.ı	Dhe	Th~	300	Val	17-1	Dro	Ile
50	305			501	Дуо	310	Olu	Giu	пец	FIIC	315	GIY	vai	vaı	PIO	320
	Leu	Val	Glu	Leu	Asp		Asp	Val	Asn	Gly		Lys	Phe	Ser	Val	
					325					330					335	
				340					345			Leu		350		
55	Ile	Cys	Thr 355	Thr	Gly	ГЛЗ	Leu	Pro 360	Val	Pro	Trp	Pro	Thr 365	Leu	Val	Thr

209

	Thr	Leu	Thr	Tvr	Glv	Val	Gln	Cvs	Phe	Ser	Ara	Tvr	Pro	αsA	His	Met	
		370		_	-		375	-			_	380		_			
	Lys 385	Gin	His	Asp	Phe	90 390	ьуs	Ser	Ala	Met	Pro 395	Glu	GIÀ	Tyr	Val	400	
5	Glu	Arg	Thr	Ile	Phe 405	Phe	Lys	Asp	Asp	Gly 410	Asn	Tyr	Lys	Thr	Arg 415	Ala	
	Glu	Val	Lys	Phe 420	Glu	Gly	Asp	Thr	Leu 425	Val	Asn	Arg	Ile	Glu 430	Leu	Lys	
10	Gly	Ile	Asp 435	Phe	Lys	Glu	Asp	Gly 440	Asn	Ile	Leu	Gly	His 445	Lys	Leu	Glu	
10	Tyr	Asn 450		Asn	Ser	His	Asn 455		Tyr	Ile	Met	Ala 460		Lys	Gln	Lys	
			Ile	Lys	Val			Lys	Ile	Arg			Ile	Glu	Asp		
15	465 Ser	Val	Gln	Leu	Ala	470 Asp	His	Tvr	Gln	Gln	475 Asn	Thr	Pro	Ile	Gly	480 Asp	
					485	_		_		490					495		
	_			500					505	_				510	Ser		
20	Leu	Ser	Lys 515	Asp	Pro	Asn	Glu	Lys 520	Arg	Asp	His	Met	Val 525	Leu	Leu	Glu	
	Phe		Thr	Ala	Ala	Gly		Thr	Leu	Gly	Met		Glu	Leu	Tyr	Lys	
		530					535					540					
25			(2)	INI	FORM	TION	1 FOI	R SE	QI Q	NO:	114:						
20		(:	i) SI	-													
				LENG TYPI				_	airs								
			(C)	STR	ANDE	ONES	S: s:	ingl	<b>e</b>								
30			(D)	TOP	OLOG.	Y: 1:	inea	r									
		-	ii) 1 ix) 1			TYPI	E: cl	DNA									
35			(A)	) NAI	ME/K	EY: (	Codi	na S	eaue:	nce							
			(B)	) LO	CATI	ON:	1:	1632	1								
			(D	) OT	HER	INFO	RMAT.	ION:									
40		(:	xi) :	SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	114:					
40																CTG	48
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu	
45																GGC Gly	96
				20	-	-			25		•			30			•
																ATC	144
50	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
	тсс	מככ	ልሮሮ	GGC	ממ	ርጥር	כככ	ርጥር	כככ	ጥርር	. ררי	י ארר	רידר	GTC	. ארר	ACC	192
		Thr					Pro					Thr				Thr	
55		50					55					60					

						AGC Ser							240
5						ATG Met							288
10						GGC Gly 105							336
15						GTG Val							384
20						ATC Ile							432
						ATC Ile							480
25						CGC Arg							528
30						CAG Gln 185							576
35	_					TAC Tyr					_		624
40						GAT Asp							672
						GGC							720
45				Ala		AAC Asn		Gln				Ile	768
50			Tyr				Lys				Leu	ACG Thr	816
55		Val				Ile				Glu		GAG Glu	864

										211							
	GGT Gly	GTG Val 290	CCC Pro	AGT Ser	ACT Thr	GCC Ala	ATC Ile 295	CGA Arg	GAG Glu	ATC Ile	TCT Ser	CTG Leu 300	CTT Leu	AAG Lys	GAG Glu	CTT Leu	912
5	AAC Asn 305	CAT His	CCT Pro	AAT Asn	ATT Ile	GTC Val 310	AAG Lys	CTG Leu	CTG Leu	GAT Asp	GTC Val 315	ATT Ile	CAC His	ACA Thr	GAA Glu	AAT Asn 320	960
10	Lys	Leu	Tyr	CTG Leu	Val 325	Phe	Glu	Phe	Leu	His 330	Gln	Asp	Leu	Lys	Lys 335	Phe	1008
15	Met	Asp	Ala	TCT Ser 340	Ala	Leu	Thr	Gly	Ile 345	Pro	Leu	Pro	Leu	Ile 350	Lys	Ser	1056
20	TAT Tyr	CTG Leu	TTC Phe 355	CAG Gln	CTG Leu	CTC Leu	CAG Gln	GGC Gly	CTA Leu	GCT Ala	TTC Phe	TGC Cys	CAT His 365	TCT Ser	CAT His	CGG Arg	1104
	GTC Val	CTC Leu 370	CAC His	CGA Arg	GAC Asp	CTT Leu	AAA Lys 375	CCT Pro	CAG Gln	AAT Asn	CTG Leu	CTT Leu 380	ATT Ile	AAC Asn	ACA Thr	GAG Glu	1152
25	GGG Gly 385	GCC Ala	ATC Ile	AAG Lys	CTA Leu	GCA Ala 390	GAC Asp	TTT Phe	GGA Gly	CTA Leu	GCC Ala 395	AGA Arg	GCT Ala	TTT Phe	GGA Gly	GTC Val 400	1200
30	CCT Pro	GTT Val	CGT Arg	ACT Thr	TAC Tyr 405	ACC Thr	CAT His	GAG Glu	GTG Val	GTG Val 410	ACC Thr	CTG Leu	TGG Trp	TAC Tyr	CGA Arg 415	GCT Ala	1248
35	CCT Pro	GAA Glu	ATC Ile	CTC Leu 420	CTG Leu	GGC Gly	TCG Ser	AAA Lys	TAT Tyr 425	TAT Tyr	TCC Ser	ACA Thr	GCT Ala	GTG Val 430	GAC Asp	ATC Ile	1296
40	TGG Trp	AGC Ser	CTG Leu 435	GGC Gly	TGC Cys	ATC Ile	TTT Phe	GCT Ala 440	GAG Glu	ATG Met	GTG Val	ACT Thr	CGC Arg 445	CGG Arg	GCC Ala	CTG Leu	1344
	TTC Phe	CCT Pro 450	GGA Gly	GAT Asp	TCT Ser	GAG Glu	ATT Ile 455	GAC Asp	CAG Gln	CTC Leu	TTC Phe	CGG Arg 460	ATC Ile	TTT Phe	CGG Arg	ACT Thr	1392
45	CTG Leu 465	GGG Gly	ACC Thr	CCA Pro	GAT Asp	GAG Glu 470	GTG Val	GTG Val	TGG Trp	CCA Pro	GGA Gly 475	GTT Val	ACT Thr	TCT Ser	ATG Met	CCT Pro 480	1440
50				CCA Pro													1488
55	GTT Val	GTA Val	CCT Pro	CCC Pro 500	CTG Leu	GAT Asp	GAA Glu	GAT Asp	GGA Gly 505	CGG Arg	AGC Ser	TTG Leu	TTA Leu	TCG Ser 510	CAA Gln	ATG Met	1536

212

CTG CAC TAC GAC CCT AAC AAG CGG ATT TCG GCC AAG GCA GCC CTG GCT Leu His Tyr Asp Pro Asn Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala 520 515 CAC CCT TTC TTC CAG GAT GTG ACC AAG CCA GTA CCC CAT CTT CGA CTC T 1633 5 His Pro Phe Phe Gln Asp Val Thr Lys Pro Val Pro His Leu Arg Leu 535 1635 GA 10 (2) INFORMATION FOR SEQ ID NO:115: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 544 amino acids 15 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein 20 (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:115: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 25 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 55 60 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 35 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 40 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 45 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 190 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 50 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 235 Gly Leu Arg Ser Arg Ala Met Glu Asn Phe Gln Lys Val Glu Lys Ile 55 250 Gly Glu Gly Thr Tyr Gly Val Val Tyr Lys Ala Arg Asn Lys Leu Thr

```
260
                                      265
                                                          270
      Gly Glu Val Val Ala Leu Lys Lys Ile Arg Leu Asp Thr Glu Thr Glu
                                  280
      Gly Val Pro Ser Thr Ala Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu
 5
                              295
      Asn His Pro Asn Ile Val Lys Leu Leu Asp Val Ile His Thr Glu Asn
                          310
                                              315
      Lys Leu Tyr Leu Val Phe Glu Phe Leu His Gln Asp Leu Lys Lys Phe
                     325
                                         330
10
      Met Asp Ala Ser Ala Leu Thr Gly Ile Pro Leu Pro Leu Ile Lys Ser
                  340
                                     345
      Tyr Leu Phe Gln Leu Leu Gln Gly Leu Ala Phe Cys His Ser His Arg
                                  360
      Val Leu His Arg Asp Leu Lys Pro Gln Asn Leu Leu Ile Asn Thr Glu
15
                              375
     Gly Ala Ile Lys Leu Ala Asp Phe Gly Leu Ala Arg Ala Phe Gly Val
                          390
                                              395
      Pro Val Arg Thr Tyr Thr His Glu Val Val Thr Leu Trp Tyr Arg Ala
                      405
                                          410
20
      Pro Glu Ile Leu Leu Gly Ser Lys Tyr Tyr Ser Thr Ala Val Asp Ile
                                      425
      Trp Ser Leu Gly Cys Ile Phe Ala Glu Met Val Thr Arg Arg Ala Leu
                                  440
      Phe Pro Gly Asp Ser Glu Ile Asp Gln Leu Phe Arg Ile Phe Arg Thr
25
                              455
      Leu Gly Thr Pro Asp Glu Val Val Trp Pro Gly Val Thr Ser Met Pro
                          470
                                              475
     Asp Tyr Lys Pro Ser Phe Pro Lys Trp Ala Arg Gln Asp Phe Ser Lys
                      485
                                         490
30
     Val Val Pro Pro Leu Asp Glu Asp Gly Arg Ser Leu Leu Ser Gln Met
                                      505
     Leu His Tyr Asp Pro Asn Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala
                                  520
     His Pro Phe Phe Gln Asp Val Thr Lys Pro Val Pro His Leu Arg Leu
35
         530
                                                  540
               (2) INFORMATION FOR SEQ ID NO:116:
            (i) SEQUENCE CHARACTERISTICS:
40
              (A) LENGTH: 2532 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
45
            (ii) MOLECULE TYPE: cDNA
            (ix) FEATURE:
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2529
50
               (D) OTHER INFORMATION:
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:
     ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG
                                                                            48
55
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
                       5
                                          1.0
```

5											GTG Val 30			96
J	 			 							AAG Lys			144
10											GTG Val	_	_	192
15											CAC His			240
20											GTC Val	_		288
25											CGC Arg 110	_	_	336
											CTG Leu			384
30											CTG Leu			432
35											CAG Gln			480
40											GAC Asp			528
45											GGC Gly 190			576
45			Leu				Tyr				TCC Ser			624
50		Asp				Arg				Leu	CTG Leu			672
55	Thr				Thr				Glu		TAC Tyr			720

5			TCT Ser	_							768
3			CTG Leu 260								816
10			CTG Leu								<b>864</b>
15			AGG Arg								912
20			TTC Phe								960
25			GTG Val								1008
			ACC Thr 340								1056
30			GAG Glu							_	1104
35			CTG Leu								1152
40			AGC Ser								1200
45			GCT Ala								1248
43	-		GAG Glu 420		-	_	 	 	_		1296
50			ACG Thr							GAG Glu	1344
55			GGC Gly					Tyr		ACG Thr	1392

5	AGG Arg 465																1440
	AAG Lys																1488
10	GAG Glu																1536
15	GGG Gly					AAC Asn											1584
20						CGA Arg											1632
25						ATC Ile 550											1680
25						GCT Ala											1728
30					Asn	GAC Asp											1776
35				Val		ACC Thr			Glu							AAA Lys	1824
40			Pro					Val					Ala			CCC Pro	1872
45		Ser					Gly					Thr				CTC Leu 640	1920
45						Ser					gly					GAG Glu	1968
50					: Glr					Pro					Pro	AGT Ser	2016
55				g Gly					e Lei					ı Glı		G CAG g Gln	2064

5	GAA Glu	AGT Ser 690	CTG Leu	CCT Pro	CAC His	GCA Ala	GGG Gly 695	CCC Pro	ATC Ile	ATC Ile	GTG Val	CAC His 700	TGC Cys	AGC Ser	GCC Ala	GGC Gly	2112
	ATC Ile 705	GGC Gly	CGC Arg	ACA Thr	GGC Gly	ACC Thr 710	ATC Ile	ATT Ile	GTC Val	ATC Ile	GAC Asp 715	ATG Met	CTC Leu	ATG Met	GAG Glu	AAC Asn 720	2160
10	ATC Ile	TCC Ser	ACC Thr	AAG Lys	GGC Gly 725	CTG Leu	GAC Asp	TGT Cys	GAC Asp	ATT Ile 730	GAC Asp	ATC Ile	CAG Gln	AAG Lys	ACC Thr 735	ATC Ile	2208
15	Gln	Met	Val	CGG Arg 740	Ala	Gln	Arg	Ser	Gly 745	Met	Val	Gln	Thr	Glu 750	Ala	Gln	2256
20	Tyr	Lys	Phe 755	ATC Ile	Tyr	Val	Ala	Ile 760	Ala	Gln	Phe	Ile	Glu 765	Thr	Thr	Lys	2304
25	Lys	Lys 770	Leu	GAG Glu	Val	Leu	Gln 775	Ser	Gln	Lys	Gly	Gln 780	Glu	Ser	Glu	Tyr	2352
	Gly 785	Asn	Ile	ACC Thr	Tyr	Pro 790	Pro	Ala	Met	Lys	Asn 795	Ala	His	Ala	Lys	Ala 800	2400
30	TCC Ser	CGC Arg	ACC Thr	TCG Ser	TCC Ser 805	AAA Lys	CAC His	AAG Lys	GAG Glu	GAT Asp 810	GTG Val	TAT Tyr	GAG Glu	AAC Asn	CTG Leu 815	CAC His	2448
35	ACT Thr	AAG Lys	AAC Asn	AAG Lys 820	AGG Arg	GAG Glu	GAG Glu	AAA Lys	GTG Val 825	AAG Lys	AAG Lys	CAG Gln	CGG Arg	TCA Ser 830	GCA Ala	GAC Asp	2496
40				AGC Ser								TGA					2532
			(2)	INE	FORMA	AOITA	ı FOF	SE(	) ID	NO:1	.17:						
45		( i	(A) (B)	QUEN LENC TYPE	TH: E: an	843 mino	amir acid	io ad	cids								
50			(D) .i) M	TOPO OLEC LAGME	ULE	7: li TYPE	near E: pr	otei	ın								
55	Met			EQUE Lys									Val	Pro	Ile	Leu	<b>.</b>

	1				5					10					15	
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
5	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	65			_		70		Phe			75					80
10					85			Ala		90					95	
				100				Asp	105					110		
15		-	115		_			Leu 120					125			
		130					135	Asn				140				
	145	_				150		Tyr			155					160
20					165			Ile		170					175	
				180				Gln	185					190		
25			195					His 200					205			
		210	_				215	Arg				220				
00	225				_	230		Leu			235					240
30	_				245			Leu		250					255	
				260				Thr	265					270		
35			275					Ser 280					285			
		290					295					300				
40	305					310		Tyr Thr			315					320
40					325					330					335	
				340				Leu His	345					350		
45			355					360 Gly					365			
		370	)				375					380	)			
<b>E</b> O	385					390	)	, Asp , Ser			395	5				400
50					405	;				410	)				415	5
				420	l .			Tyr l Glu	425	5				430	)	
55	Asp		435					440	)				445	5		

```
450
                             455
                                                  460
     Arg Val Asn Ala Ala Asp Ile Glu Asn Arg Val Leu Glu Leu Asn Lys
                  470
                                             475
     Lys Gln Glu Ser Glu Asp Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe
5
                     485
                                         490
     Glu Ser Leu Gln Lys Gln Glu Val Lys Asn Leu His Gln Arg Leu Glu
                                     505
     Gly Gln Arg Pro Glu Asn Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu
                                 520
                                                     525
10
     Pro Phe Asp His Ser Arg Val Ile Leu Gln Gly Arg Asp Ser Asn Ile
                             535
                                                 540
     Pro Gly Ser Asp Tyr Ile Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu
                         550
                                             555
     Gly Pro Asp Glu Asn Ala Lys Thr Tyr Ile Ala Ser Gln Gly Cys Leu
15
                     565
                                         570
     Glu Ala Thr Val Asn Asp Phe Trp Gln Met Ala Trp Gln Glu Asn Ser
                                     585
     Arg Val Ile Val Met Thr Thr Arg Glu Val Glu Lys Gly Arg Asn Lys
                                 600
20
     Cys Val Pro Tyr Trp Pro Glu Val Gly Met Gln Arg Ala Tyr Gly Pro
                             615
     Tyr Ser Val Thr Asn Cys Gly Glu His Asp Thr Thr Glu Tyr Lys Leu
                         630
                                             635
     Arg Thr Leu Gln Val Ser Pro Leu Asp Asn Gly Asp Leu Ile Arg Glu
25
                     645
                                         650
     Ile Trp His Tyr Gln Tyr Leu Ser Trp Pro Asp His Gly Val Pro Ser
                                     665
     Glu Pro Gly Gly Val Leu Ser Phe Leu Asp Gln Ile Asn Gln Arg Gln
                                 680
30
     Glu Ser Leu Pro His Ala Gly Pro Ile Ile Val His Cys Ser Ala Gly
                             695
     Ile Gly Arg Thr Gly Thr Ile Ile Val Ile Asp Met Leu Met Glu Asn
                         710
                                              715
     Ile Ser Thr Lys Gly Leu Asp Cys Asp Ile Asp Ile Gln Lys Thr Ile
35
                     725
                                          730
     Gln Met Val Arg Ala Gln Arg Ser Gly Met Val Gln Thr Glu Ala Gln
                                     745
     Tyr Lys Phe Ile Tyr Val Ala Ile Ala Gln Phe Ile Glu Thr Thr Lys
                                 760
40
     Lys Lys Leu Glu Val Leu Gln Ser Gln Lys Gly Gln Glu Ser Glu Tyr
                             775
                                                  780
     Gly Asn Ile Thr Tyr Pro Pro Ala Met Lys Asn Ala His Ala Lys Ala
                         790
     Ser Arg Thr Ser Ser Lys His Lys Glu Asp Val Tyr Glu Asn Leu His
45
                     805
                                         810
     Thr Lys Asn Lys Arg Glu Glu Lys Val Lys Lys Gln Arg Ser Ala Asp
                                     825
     Lys Glu Lys Ser Lys Gly Ser Leu Lys Arg Lys
50
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(2) INFORMATION FOR SEQ ID NO:118:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2562 base pairs
- (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single

PCT/DK98/00145 WO 98/45704

220

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
- (B) LOCATION: 1...2559
- (D) OTHER INFORMATION:

10		(x	i) S	EQUE	NCE	DESC	RIPI	: NOI	SEQ	ID	NO:1	18:					
45		CTG Leu														_	48
15		ACC Thr															96
20		AGT Ser															144
25		CAG Gln 50															192
30		тат туг															240
35		ACT Thr															288
33		CTC Leu															336
40		CAT His															384
45								Leu					Leu			CCT Pro	432
50		Asp					Val					Pro				CCA Pro 160	480
55						, Val					. Val					GGA Gly	528
55	CGC	TAC	: ACA	GTG	GGI	GGT	TTO	GAG	ACC	TTC	GAC	AGC	CTC	ACG	GAG	C CTG	576

	Arg	Tyr	Thr	Val 180	Gly	Gly	Leu	Glu	Thr 185	Phe	Asp	Ser	Leu	Thr 190	Asp	Leu	
5									ATT Ile								624
10									GCC Ala								672
45									AAC Asn								720
15	-								GAG Glu								768
20									CTG Leu 265								816
25									ATT Ile								864
30									AAC Asn							_	912
0.5									CTG Leu							_	960
35									TGT Cys								1008
40									AAC Asn 345								1056
45									AAC Asn								1104
50			Gly					Tyr	GGG Gly				Val				1152
		Glu					Glu		AAA Lys			Thr					1200
55	ררפ	רידוני.	ርአሮ	א מ	GGA	GAC	ריתי	. איזייני ע	CCC	ርአሮ	! ልጥር	ጥርር	! ሮልጥ	י מיזי	י ראמ	ሞልሮ	1248

	Pro	Leu	Asp	Asn	Gly	Asp	Leu	Ile	Arg	Glu	Ile	Trp	His	Tyr	Gln	Tyr	
					405					410					415		
5						CAT His											1296
				420					425					430			
						ATC Ile											1344
10			435	<b>L</b>				440	<b>J</b>				445				
						CAC His											1392
15	Uly	450	110	110	Vul	1125	455	JCI	ALU	GIY	110	460	9	1112	CLY		
13						ATG Met											1440
	465	116	vai	116	Asp	470	Беп	MEC	Giu	ASII	475	361	IIII	пуъ	Gry	480	
20						ATC											1488
	Asp	Cys	Asp	116	485	Ile	GIN	ьys	Thr	490	GIN	Met	vaı	Arg	495	GIII	
25						CAG										_	1536
25	Arg	ser	GIY	мес 500	vai	Gln	Thr	GIU	505	GIn	Tyr	гуѕ	Pne	510	Tyr	vai	
						ATT											1584
30	Ala	Ile	515	GIn	Phe	Ile	GIu	Thr 520	Thr	Lys	Lys	гÀг	ьеи 525	GIU	vaı	Leu	
						CAG											1632
	Gln	Ser 530	GIn	Lys	GIY	Gln	G1u 535	Ser	Glu	Tyr	GIÀ	Asn 540	He	Thr	Tyr	Pro	
35																AAA	1680
	Pro 545	Ala	Met	Lys	Asn	Ala 550	His	Ala	ГÀЗ	Ala	Ser 555	Arg	Thr	Ser	Ser	Lys 560	
40						TAT											1728
	His	Lys	Glu	Asp	Val 565	Tyr	Glu	Asn	Leu	His 570		Lys	Asn	Lys	Arg 575		
	GAG	AAA	GTG	AAG	AAG	CAG	CGG	TCA	GCA	GAC	AAG	GAG	AAG	AGC	AAG	GGT	1776
45	Glu	Lys	Val	Lys 580	_	Gln	Arg	Ser	Ala 585	_	Lys	Glu	Lys	Ser 590		Gly	
	TCC	CTC	AAG	AGG	AAG	CGA	ATT	CTG	CAG	TCG	ACG	GTA	CCG	CGG	GCC	: CGG	1824
50	Ser	Leu	Lys 595	_	Lys	Arg	Ile	Leu 600		Ser	Thr	Val	Pro 605	_	Ala	Arg	
	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	agc	. AAG	GGC	' GAG	GAG	CTG	TTC	. ACC	1872
	Asp	Pro 610		Val	Ala	Thr	Met 615		Ser	Lys	Gly	Glu 620		Leu	Phe	Thr	
55	GGG	GTG	GTG	ccc	: ATC	: CTG	GTC	GAC	CTC	GAC	GGC	GAC	: GTA	L AAC	: GGC	CAC	1920

									4	223							
	Gly 625	Val	Val	Pro	Ile	Leu 630	Val	Glu	Leu	Asp	Gly 635	Asp	Val	Asn	Gly	His 640	
5						GGC Gly											1968
10						ATC Ile											2016
45						ACC Thr											2064
15	TAC Tyr	CCC Pro 690	GAC Asp	CAC His	ATG Met	AAG Lys	CAG Gln 695	CAC His	GAC Asp	TTC Phe	TTC Phe	AAG Lys 700	TCC Ser	GCC Ala	ATG Met	CCC Pro	2112
20						GAG Glu 710											2160
25						GAG Glu					Gly						2208
30					Lys	GGC Gly				Lys							2256
				Leu		TAC			Asn					Tyr			2304
35			Lys					Ile					Lys			CAC His	2352
40	AAC Asn 785	ılle	GAC	G GAC	GGC Gly	AGC Ser 790	Val	CAG Gln	CTO	GCC 1 Ala	GAC A Asp 799	His	C TAC	CAG	Gl:	AAC Asn 800	2400
45						Gly					ı Pro					C CTG c Leu	2448
50					c Ala					o Pro					J As	r CAC p His	2496
	ATC Met	G GT	C CT l Le	u Lev	G GAG	G TTO	GTO Val	3 ACC 1 Th: 840	r Al	C GC a Al	C GGG	G AT	C AC e Th 84	r Lev	C GG	C ATG y Met	2544
55	GA	C GA	G CT	G TA	C AA	G TA	Ą										2562 <b>22</b> 3

WO 98/45704

224

Asp Glu Leu Tyr Lys 850

5 (2) INFORMATION FOR SEQ ID NO:119:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 853 amino acids
  - (B) TYPE: amino acid
- 10 (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

	Met 1	Leu	Ser	Arg	Gly 5	Trp	Phe	His	Arg	Asp 10	Leu	Ser	Gly	Leu	Asp 15	Ala
20	Glu	Thr	Leu	Leu 20	Lys	Gly	Arg	Gly	Val 25	His	Gly	Ser	Phe	Leu 30	Ala	Arg
	Pro	Ser	Arg 35	Lys	Asn	Gln	Gly	Asp 40	Phe	Ser	Leu	Ser	Val 45	Arg	Val	Gly
25	Asp	Gln 50	Val	Thr	His	Ile	Arg 55	Ile	Gln	Asn	Ser	Gly 60	Asp	Phe	Tyr	Asp
	Leu 65	Tyr	Gly	Gly	Glu	Lys 70	Phe	Ala	Thr	Leu	Thr 75	Glu	Leu	Val	Glu	Tyr 80
	Tyr	Thr	Gln	Gln	Gln 85	Gly	Val	Leu	Gln	Asp 90	Arg	Asp	Gly	Thr	Ile 95	Ile
30	His	Leu	Lys	Tyr 100	Pro	Leu	Asn	Cys	Ser 105	Asp	Pro	Thr	Ser	Glu 110	Arg	Trp
	Tyr	His	Gly 115	His	Met	Ser	Gly	Gly 120	Gln	Ala	Glu	Thr	Leu 125	Leu	Gln	Ala
35	Lys	Gly 130	Glu	Pro	Trp	Thr	Phe 135	Leu	Val	Arg	Glu	Ser 140	Leu	Ser	Gln	Pro
	Gly 145	Asp	Phe	Val	Leu	Ser 150	Val	Leu	Ser	Asp	Gln 155	Pro	ГÀЗ	Ala	Gly	Pro 160
	Gly	Ser	Pro	Leu	Arg 165	Val	Thr	His	Ile	Lys 170	Val	Met	Cys	Glu	Gly 175	Gly
40	Arg	Tyr	Thr	Val 180	Gly	Gly	Leu	Glu	Thr 185	Phe	Asp	Ser	Leu	Thr 190	Asp	Leu
	Val	Glu	His 195	Phe	Lys	Lys	Thr	Gly 200	Ile	Glu	Glu	Ala	Ser 205	Gly	Ala	Phe
45	Val	Tyr 210	Leu	Arg	Gln	Pro	Tyr 215	Tyr	Ala	Thr	Arg	Val 220	Asn	Ala	Ala	Asp
	Ile 225	Glu	Asn	Arg	Val	Leu 230	Glu	Leu	Asn	Lys	Lys 235	Gln	Glu	Ser	Glu	Asp 240
	Thr	Ala	Lys	Ala	Gly 245	Phe	Trp	Glu	Glu	Phe 250	Glu	Ser	Leu	Gln	Lys 255	
50	Glu	Val	Lys	Asn 260	Leu	His	Gln	Arg	Leu 265		Gly	Gln	Arg	Pro 270	Glu	Asn
	Lys	Gly	Lys 275	Asn	Arg	Tyr	Lys	Asn 280	Ile	Leu	Pro	Phe	Asp 285		Ser	Arg
55	Val	Ile 290		Gln	Gly	Arg	Asp 295		Asn	Ile	Pro	Gly 300	Ser	Asp	Tyr	Ile
	Asn	Ala	Asn	Tyr	Ile	Lys	Asn	Gln	Leu	Leu	Gly	Pro	Asp	Glu	Asn	Ala

	305					310					315					320
	Lys	Thr	Tvr	Ile	Ala	Ser	Gln	Glv	Cvs	Leu		Ala	Thr	Va 1	Asn	
	-		2		325			<b></b> 2	0,2	330			****	•42	335	,,,,
	Dhe	Trn	Gln	Mot		Trn	Gln	C1.,	7.00		7 ~~~	1707	71.	17- 7	Met	mh
5	1 110	TIP	GIII		ALG	TLD	GIII	GIU		ser	Arg	val	TIE		Mec	THE
3	m1	3	<b>a</b> 1	340	<b>~</b> 1.		<b>~</b> 3	_	345		_		_	350		
	Inr	Arg		vaı	GIU	ьys	GIY		Asn	Lys	Cys	Val	Pro	Tyr	Trp	Pro
			355					360					365			
	Glu		Gly	Met	Gln	Arg	Ala	Tyr	Gly	Pro	Tyr	Ser	Val	Thr	Asn	Cys
		370					375					380				
10	Gly	Glu	His	Asp	Thr	Thr	Glu	Tyr	Lys	Leu	Arg	Thr	Leu	Gln	Val	Ser
	385					390					395					400
	Pro	Leu	Asp	Asn	Gly	Asp	Leu	Ile	Arg	Glu	Ile	Trp	His	Tyr	Gln	Tyr
					405				_	410		_		-	415	-
	Leu	Ser	Trp	Pro	Asp	His	Gly	Val	Pro		Glu	Pro	Glv	Glv	Val	Len
15			-	420	_		-		425				1	430		
	Ser	Phe	Leu		Gln	Tle	Asn	Gln		Gln	Glu	Ser	T.611		His	772
			435	p			11011	440	~~9	GIII	Olu	DCT		FIO	1115	MIG
	Clv	Dro		Tlo	17-1	Wie	Cara		7 J -	01	T1 -	<b>a</b> 1	445	<b>m</b> 1	<b>~</b> 1	m1
	Gry		TTE	116	vaı	птр		Ser	Ala	GTA	тте		Arg	Thr	Gly	Tnr
20	<b>7</b> 1 -	450	77 - J	~ 7			455			_		460	_		_	
20		Tie	vaı	тте	Asp		ьеи	met	Glu	Asn		Ser	Thr	Lys	Gly	
	465	_	_		_	470			_	_	475					480
	Asp	Cys	Asp	He		Ile	Gln	Lys	Thr		Gln	Met	Val	Arg	Ala	Gln
					485					490					495	
	Arg	Ser	Gly	Met	Val	Gln	Thr	Glu	Ala	Gln	Tyr	Lys	Phe	Ile	Tyr	Val
25				500					505					510		
	Ala	lle	Ala	Gln	Phe	Ile	Glu	Thr	Thr	Lys	Lys	Lys	Leu	Glu	Val	Leu
			515					520		_	_	-	525			
	Gln	Ser	Gln	Lys	Gly	Gln	Glu	Ser	Glu	Tvr	Glv	Asn	Ile	Thr	Tyr	Pro
		530		-	-		535					540			- 1 -	
30	Pro	Ala	Met	Lvs	Asn	Ala		Ala	Lvs	Δla	Ser		Thr	Ser	Ser	Live
	545					550			-1-		555	5				560
		Lvs	Glu	Asn	Val		Glu	Δen	T.e.ii	Hic		Lvc	Λcn	Two	Arg	
		_,_			565	- 7 -	014	ASII	шец	570	1111	цуз	ASII	ыyы	575	Giu
	Clu	Lve	Val	Lave		Gln	7~~	Co.~	- ות		7	<b>a</b> 1	T	0	Lys	<b>a</b> 1
35	GIU	БуБ	val	580	БуЗ	GIII	Arg	SEL		Asp	цуѕ	Giu	пуѕ		цуз	сту
50	505	Tou	T 140		T	7	<b>~</b> 1~	T	585		m1	**- 3	_	590	~ ~ -	<b>-</b>
	361	Leu		Arg	гуѕ	Arg	тте		GIn	ser	Thr	vaı		Arg	Ala	Arg
		D	595		~ ~	1		600		_			605		_	_
	Asp		Pro	vaı	Ala	Thr		Val	Ser	Lys	Gly		Glu	Leu	Phe	Thr
40		610		_			615	_				620				
40		Val	Val	Pro	Ile		Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His
	625					630					635					640
	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys
					645					650					655	
	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp
45				660					665					670		-
	Pro	Thr	Leu	Val	Thr	Thr	Leu	Thr	Tvr	Glv	Val	Gln	Cvs	Phe	Ser	Arg
			675					680	-	4			685			5
	Tvr	Pro	Asp	His	Met	Lvs	Gln		Asn	Phe	Phe	Laze		Δla	Met	Pro
	-1-	690				_,_	695	1115	21.50	11110	1110	700	501	AIG	HICE	FLO
50	Glu		Tur	17=7	Gin	G311		Thr	т 7 о	nh o	nh-		N	7	<i>α</i> 3	Asn
00	705	Gry	TAT	vai	GIII	710	Arg	THE	TIE	Pile		пуѕ	Asp	Asp	GIŞ	
		T	mb	A	77-		**- 7	<b>.</b>	D1	~1	715	_		_		720
	тАт	пур	THE	Arg		GIU	val	тÃг	rne		GIA	Asp	Tur	ьeu	Val	Asn
	7	<b>T7</b> -	<b>a</b> 1	<b>T</b>	725	<b>~</b> 3	<b>+</b> 7	_	m.1	730		_		_	735	_
EE	arg	тте	GIU		ьys	GIA	тте	Asp		гуз	Glu	Asp	Gly		Ile	Leu
55	~ 3		_	740		_		_	745					750	_	
	GIY	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met

										20								
			755					760					765					
	Ala	Asp 770	Lys	Gln	Lys .		Gly 775	Ile :	Lys '	Val 1		Phe 780	Lys	Ile	Arg	His		
_	Asn :	Ile	Glu	Asp	_		Val (	Gln :	Leu i			His	Tyr	Gln	Gln			
5	785 Thr	Dro	T10	Cl.		790	Dro '	Wall 1	T.em		795 Pro	Δen	Δen	His	ጥvr	800 Leu		
	IIII .	FIO	116	GIY	805	GIY	rio	var .		810					815			
	Ser	Thr	Gln	Ser 820	Ala	Leu	Ser		Asp 825	Pro .	Asn	Glu	Lys	Arg 830	Asp	His		
10	Met	Val	Leu 835	Leu	Glu	Phe		Thr 840	Ala	Ala	Gly	Ile	Thr 845	Leu	Gly	Met		
	Asp	Glu 850	Leu	Tyr	Lys													
15			(2)	INE	FORMA	TION	FOR	SEQ	ID	NO:1	20:							
20		<b>(</b> i	(A) (B) (C)	LENC TYPE STRA	ICE C FTH: E: nu ANDEL OLOGY	2994 Iclei NESS	bas c ac : si	e pa id ngle	irs									
25		-	ix) : (A (B	FEATU ) NAI ) LOO	CULE URE: ME/KI CATIO HER	EY: (	Codir	ng Se 2991	equer	ıce								·
30		(:	xi)	SEQU	ENCE	DESC	CRIP	rion	: SE(	) ID	NO:	120:						
25	ATG Met 1	GTG Val	AGC Ser	AAG Lys	GGC Gly 5	GAG Glu	GAG Glu	CTG Leu	TTC Phe	ACC Thr 10	GGG Gly	GTG Val	GTG Val	CCC Pro	ATC Ile 15	CTG Leu	4.8	1
35																GGC Gly	96	5
40																ATC E Ile	14	1
45																C ACC r Thr		2
50																G AAG t Lys 80		0
EE																G GAG n Glu		8
55	CGC	AC(	C AT	C TT	C TTO	C AAC	GAC	C GAC	c GGC	: AAC	C TA	C AA	G AC	C CG	C GC	C GAG	3 3 3	6 226

Arg Thr Ile Phe Phe Lys Asp Asp Gly Ash Tyr Lys Thr Arg Ala Glu 100  GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384  ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG GTG GAG TAC 115 No 115 No 120 No 125										2	227							
15		Arg	Thr	Ile		Phe	Lys	Asp	Asp		Asn	Tyr	Lys	Thr		Ala	Glu	
15		GTG	אאכ	ጥጥር	GAG	GGC	GAC	<b>ACC</b>	СТС	GTG	ממ	CGC	אדר	GAG	CTG	AAG	GGC	384
ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC  AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC ASS TY ASS SET HIS ASS VAI TY ILE MET ALA ASS LYS GIN LYS ASS 145  AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC ASS TY ASS SET HIS ASS VAI TY ILE MET ALA ASS LYS GIN LYS ASS 145  GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC GGC ATC AAG GTG GAC CAC TAC CAG CAA AAC ACC CCA ATC AGC GAC GGC AGC VAI GIN LEW ALA ASS HIS TYP GIN GIN ASS THE GIW ASS GIY SEP  20	5																	
11e Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr   130	J		-1-			1						<b>J</b>				•	-	
10		ATC	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	CTG	GGG	CAC	AAG	CTG	GAG	TAC	432
AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC AAC ASS SET HIS ASS VALUE TO THE MET ALA ASP LYS GIN LYS ASS 145 150 150 155 155 166 165 165 150 165 165 165 165 165 165 165 165 165 165		Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	
ASN TYP ASN SER HIS ASN Val Tyr Ile Met Ala ASP Lys Gln Lys Asn   160	10																	
145																		480
15   GGC   ATC   AAG   GTG   AAC   TTC   AAG   ATC   CGC   CAC   AAC   ATC   GAG   GAC   GGC   AGC   GGC   AGC   GGC   AGC			Tyr	Asn	Ser	His		Val	Tyr	Ile	Met		Asp	гуs	GIn	ràs		
GCC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC AGC GIV 11e Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 175	15	145					150					100					100	
Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 175	15	GGC	<b>አ</b> ፕሮ	AAG	GTG	አልሮ	ጥጥር	מממ	אידר	CGC	ראַכ	ΔAC	ATC	GAG	GAC	GGC	AGC	528
165   170   175   175   176   175   176																		
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 190		O.J		-,-				-1-						-	-			
Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 190																		
185   190   185   190   195   190   195   190   195   190   195   190   195   195   190   195	20																	576
25 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 205  AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672  AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC 672  Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215  GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 240  GGA CTC AGA TCT CGA GCT CAA GCT TCC AAT TCG ACC ATG GAC CTG TAC AAG TCC 720  GGA CTC AGA TCT CGA GCT CAA GCT TCC AAT TCG ACC ATG GAC GAG CGG CCC 768  GGY Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro Gly Leu Arg Pro Gly Ala Gly Gly Gly Pro Trp Glu Met Arg Glu Arg Pro Gly Ala Gly Gly Gly Pro Trp Glu Met Arg Glu Arg 270  CTG GGC ACC GGC GGC GGC GGC GGC GGC CGG GGC CCC TGG CAC ATG GAC CAT CGG GAA Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 285  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC ACC ACC CAC CAC CAC CAC CAC CAC CA		Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile		Asp	Gly	
25  Pro Val Leu Leu Pro Asp Asp His Tyr Leu Ser Thr Gln Ser Ala Leu 205					180					185					190			
25  Pro Val Leu Leu Pro Asp Asp His Tyr Leu Ser Thr Gln Ser Ala Leu 205		ccc	стс	CTG	CTG	CCC	CNC	አአሮ	CAC	ሞልሮ	כידיני	AGC	ACC	CAG	TCC	GCC	CTG	624
AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 210  GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAG GAG CTG TAC AAG TCC Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 240  GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG GAG CGG CCC Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 255  CCG GGG CTG CGG CCG GGC GCC GGC GGC GGC	25																	021
AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC ATG GTC CTG CTG GAG TTC Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 210  GTA ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 225  GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG GAG CGG CCC Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 275  CCG GGG CTG CGG CGG GGC GGC GGC GGC CCC TGG GAG ATG CGG GAG CGG ARG Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 270  CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA ATG CGG CAC Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 285  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC 285  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC 2912  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 320  55	20	110	Vul							-1-								
Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 210  GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 225  GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG GAG CGG CCC Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 245  40  CCG GGG CTG CGG CCG GGC GCG GGC GGC GGC																		
STG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC   Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 240																		672
GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TCC Val Thr Ala Ala Gly Tle Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 225  GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG GAG CGG CCC Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 255  CCG GGG CTG CGG CCG GGC GGC GGC GGC CCC TGG GAG ATG CGG GAG CGG CCC Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 265  CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA ATG CGG CAC CGG CGC CTG GGA ATG CGG CAC CGG CGG CGC CTG GGA ATG CGG GAA ATG CGG GAG CGG CCC TGG GAG ATG CGG GAG CGG CGC CTG GAG ATG CGG GAG CGG CGC CTG GAG ATG CGG GAA ATG CGG CTA GAG CAT CGG GAA ATG CGG CTA GAG CTC TGT CTG TAC CAG CAT CGG GAA ATG CGG CTA AGT ACC 285  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC 285  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC 285  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC 285  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG 296  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG 305  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG 305  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG 305  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG 320  55		Ser	Lys	Asp	Pro	Asn	Glu		Arg	Asp	His	Met		Leu	Leu	Glu	Phe	
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 240  35  GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG GAG CGG CCC Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 245  40  CCG GGG CTG CGG CCG GGC GGC GGC GGC GGC	30		210					215					220					
Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 240  35  GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG GAG CGG CCC Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 245  40  CCG GGG CTG CGG CCG GGC GGC GGC GGC GGC		ama	א כיכי	ccc	ccc	ccc	איזיכי	א כיתי	CTC	ccc	አጥሮ	CAC	GNG	CTG	тъс	ΔΔG	ጥሮሮ	720
225  GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG GAG CGG CCC Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 245  40  CCG GGG CTG CGG CCG GGC GGC GGC GGG CCC TGG GAG ATG CGG GAG CGG Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 260  CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 275  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  55																		, 20
GGA CTC AGA TCT CGA GCT CAA GCT TCG AAT TCG ACC ATG GAG CGG CCC Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 255  40 CCG GGG CTG CGG CCG GGC GGC GGC GGG CCC TGG GAG ATG CGG GAG CGG Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 260  CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 275  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Ser Thr 290  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Ser Thr 300  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  55						,				011					-1-			
Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 255  40 CCG GGG CTG CGG CCG GGC GGC GGC GGC CCC TGG GAG ATG CGG GAG CGG Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 260  CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 275  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  55	35																	
245  250  255  40 CCG GGG CTG CGG CCG GGC GCG GGC GGC GCG CCC TGG GAG ATG CGG GAG CGG GAG CGG Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 260  CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 275  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  55																		768
40 CCG GGG CTG CGG CCG GGC GGC GGC GGC CCC TGG GAG ATG CGG GAG CGG Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 260 Z265 Z270  CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA 45 Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 275 Z80 Z85  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290 Z95 300  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305 310 315 320  55		Gly	Leu	Arg	Ser	Arg	Ala	Gln	Ala	Ser	Asn	Ser	Thr	Met	Glu		Pro	
Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 265  CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 285  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  55						245					250					255		
Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 265  CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 285  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  55	40	ccc	CCC	OTTC	ccc	ccc	ccc	ccc	ccc	ccc	ccc	TOC	. GNG	አጥር	ccc	GAG	CGG	816
CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA  45 Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 275  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  55	40																	010
CTG GGC ACC GGC GGC TTC GGG AAC GTC TGT CTG TAC CAG CAT CGG GAA Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 275  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  55		rio	GIY	LCu			OLY	niu	Cly				<u> </u>				٠ ح	
Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu 285  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  310  315  320																		
275  CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  310  285  912  960  960  960  955		CTG	GGC	ACC	GGC	GGC	TTC	GGG	AAC	GTC	TGT	CTG	TAC	CAG	CAT	CGG	GAA	864
CTT GAT CTC AAA ATA GCA ATT AAG TCT TGT CGC CTA GAG CTA AGT ACC Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr 290 295 300  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305 310 315 320	45	Leu	Gly	Thr	Gly	Gly	Phe	Gly	Asn	Val	Cys	Leu	Tyr	Gln	His	Arg	Glu	
Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr  290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  310  310  315  320				275					280					285				
Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr  290  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305  310  310  315  320			a	ama.		3	~~~	3 mm			mam	000		<b>an a</b>	- CITE N	2 (1)	י אכפי	912
295 300  AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305 310 315 320																		212
AAA AAC AGA GAA CGA TGG TGC CAT GAA ATC CAG ATT ATG AAG AAG TTG Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305 310 315 320	50	Leu	_	Deu	цуѕ	116	ALA		_	261	Cys	AL C			ПСС	· DCI		
Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu 305 310 315 320 55	50																	
305 310 315 320 55		AAA	AAC	AGA	GAA	CGA	TGG	TGC	CAI	GAA	ATC	CAC	ATI	ATO	AAG	AAC	TTG	960
55		Lys	Asn	Arg	Glu	Arg	Trp	Cys	His	Glu	Ile	Glr	ılle	Met	Lys	Lys		
		305					310					315	5				320	
AAC CAT GCC AAT GII GTA AAG GCC TGT GAT GTT CCT GAA GAA TIG AAI 1008	55	*	. ~	~~~		, cm-							n aaa	, ,,,,		, mm-	ייי א א	1000
		AAC	CAT	GCC	AAT	G1"1	GTA	AAG	GCC	. 1GT	GA'I	. GT"	i CCI	. GAA	A GAF	7 IIC	WHI	1000

									-	220								
	Asn	His	Ala	Asn	Val 325	Val	Lys	Ala	Cys	Asp 330	Val	Pro	Glu		Leu 335	Asn		
5			ATT Ile					Leu					Tyr				1056	
10			CTC Leu 355														1104	
15			AGC Ser														1152	
15			TTG Leu														1200	
20			GTT Val														1248	
25			GGA Gly														1296	
30			GGA Gly 435														1344	
35	CCT Pro	TAC Tyr 450	Thr	GCC Ala	ACT Thr	GTT Val	GAT Asp 455	TAT Tyr	TGG	AGC Ser	TTT Phe	GGG Gly 460	Thr	ATG Met	GTA Val	TTT Phe	1392	
33	GAA Glu 465	Суя	T ATT	GCT Ala	GGA Gly	TAT Tyr 470	Arg	CCT Pro	TTT Phe	TTG Leu	CAT His	His	CTG Leu	CAG Gln	CCA Pro	TTT Phe 480	1440	
40						Ile					Pro					GCA Ala	1488	
45					: Ser					g Phe					ı Pro	CAA Gln	1536	
50				: Le					e Vai					ı Ası		G CTA p Leu	1584	
EE			u Mei					Pro					y Gl			r GAC l Asp	1632	
55	CT'	T AC	T TT	AA E	G CA	g CC	A AG	A TG	т тт	T GT	A TT.	TA A	'G GA'	r CA	C AT	T TTG	1680	228

229

	Leu 545	Thr	Leu	Lys	Gln	Pro 550	Arg	Cys	Phe	Val	Leu 555	Met	Asp	His	Ile	Leu 560	
5												TCT Ser					1728
10												TCA Ser					1776
												CAA Gln					1824
15												GCC Ala 620					1872
20-												GTT Val					1920
25												TCC Ser					1968
30												ATA					2016
				Arg					Glu			CAC His		Val			2064
35			Glu					Leu				CAA Gln 700	Arg			ATG Met	2112
40	TTA Leu 705	Ser	CTT Leu	CTT Leu	AGA Arg	TAT Tyr 710	Asn	GCT Ala	' AAC Asn	TTA	ACA Thr	Lys	ATG Met	AAG Lys	AAC Asn	ACT Thr 720	2160
45						Glr					ı Lys					CAC His	2208
50	AAA Lys	AGC Ser	ATT	CAC Glr 740	ı Lev	GAC Asp	TTO Lev	GAC Glu	AGA Arg 745	Ty:	C AGO	GAC	G CAC	3 ATC 1 Met 750	Thi	TAT	2256
				s Sei					ь Гуз					Met د		A GAA ı Glu	2304
55	AAC	G GC	TA C	CAC	TAT	r gc:	GAC	G GT	r gg:	r GT	C AT	r gg	ATA	CTC	G GA	G GAT	2352

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	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775	Val	Gly	Val	Ile	Gly 780	Tyr	Leu	Glu	Asp	
5					TTG Leu												2400
10					CAG Gln 805												2448
15					AAG Lys												2496.
15					GAG Glu												2544
20					CTC Leu												2592
25					AAG Lys												2640
30					AAA Lys 885												2688
35					GAA Glu												2736
35				Arg	TCT Ser				Ser					Ala			2784
40			Thr		GCA Ala								Glu				2832
45		Leu					Thr					Glu				CAA Gln 960	2880
50						Leu					His					ATT Elle	2928
					Glu					Ser					ı Ası	TGG Trp	2976
55	AGT	TGC	TT?	A ACA	A GAF	A TG	Ā										2994 <b>23</b> 0

231

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Ser Trp Leu Thr Glu
        995
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5 (2) INFORMATION FOR SEQ ID NO:121: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 997 amino acids (B) TYPE: amino acid 10 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 15 (xi) SEQUENCE DESCRIPTION: SEO ID NO:121: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 20 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys

70

150

230

215

295

85

Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu

Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr

Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn

Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser

Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200

280 Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr

90

170

155

Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 220 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 250 Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 265 Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu

Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu

30

35

40

45

50

										252						
	305					310					315					320
	Asn	His	Ala	Asn	Val 325	Val	Lys	Ala	Cys	Asp		Pro	Glu	Glu	Leu	
5	Ile	Leu	Ile	His 340		Val	Pro	Leu			Met	Glu	Tyr		335 Ser	Gly
Ü	Gly	Asp			Lys	Leu	Leu		345 Lys	Pro	Glu	Asn		350 Cys	Gly	Leu
	Lys		355 Ser	Gln	Ile	Leu	Ser	360 Leu	Leu	Ser	Asp	Ile	365 Gly	Ser	Gly	Ile
10	Arg	370 Tyr	Leu	His	Glu	Asn	375 Lys	Ile	Ile	His	Arg	380 Asp	Leu	Lys	Pro	Glu
	385					390					395					400
					405					410					Ile 415	
15				420					425					430	Thr	
	Phe	Val	Gly 435	Thr	Leu	Gln	Tyr	Leu 440	Ala	Pro	Glu	Leu	Phe 445	Glu	Asn	Lys
	Pro	Tyr 450	Thr	Ala	Thr	Val	Asp 455	Tyr	Trp	Ser	Phe	Gly 460	Thr	Met	Val	Phe
20	Glu 465	Cys	Ile	Ala	Gly	Tyr 470	Arg	Pro	Phe	Leu	His	His	Leu	Gln	Pro	Phe 480
	Thr	Trp	His	Glu	Lys 485	Ile	Lys	Lys	Lys	Asp 490	Pro	Lys	Cys	Ile	Phe 495	Ala
25	Cys	Glu	Glu	Met 500	Ser	Gly	Glu	Val	Arg 505	Phe	Ser	Ser	His	Leu 510	Pro	Gln
	Pro	Asn	Ser 515	Leu	Cys	Ser	Leu	Ile 520		Glu	Pro	Met	Glu 525		Trp	Leu
	Gln	Leu 530	Met	Leu	Asn	Trp	Asp 535		Gln	Gln	Arg	Gly 540		Pro	Val	Asp
30	Leu 545		Leu	Lys	Gln	Pro 550		Сув	Phe	Val	Leu 555		Asp	His	Ile	Leu 560
		Leu	Lys	Ile	Val 565		Ile	Leu	Asn	Met 570		Ser	Ala	Lys	Ile 575	
35	Ser	Phe	Leu	Leu 580		Pro	Asp	Glu	Ser 585		His	Ser	Leu	Gln 590	Ser	Arg
	Ile	Glu	Arg 595		Thr	Gly	Ile	Asn 600		Gly	Ser	Gln			Leu	Ser
	Glu	Thr 610		Ile	Ser	Leu			Arg	Lys	Pro		605 Ser	Gln	Cys	Val
40			Gly	Val	Arg		615 Cys	Asp	Ser	Tyr	Met	620 Val	Tyr	Leu	Phe	Asp
	625	G	<b>*</b>	mb	**. 3	630			_		635	_				640
					645					650					655	Ser
45				660					665					670	Pro	
			675					680					685		Ser	
	Leu	Lys 690	Glu	Asp	Tyr	Ser	Arg 695	Leu	Phe	Gln	Gly	Gln 700	Arg	Ala	Ala	Met
50	Leu 705	Ser	Leu	Leu	Arg	Tyr 710	Asn	Ala	Asn	Leu	Thr 715	Lys	Met	Lys	Asn	Thr 720
	Leu	Ile	Ser	Ala	Ser 725	Gln	Gln	Leu	Lys	Ala 730		Leu	Glu	Phe	Phe	
55	Lys	Ser	Ile	Gln 740	Leu	Asp	Leu	Glu	Arg 745		Ser	Glu	Gln	Met 750	Thr	туr
	Gly	Ile	Ser	Ser	Glu	Lys	Met	Leu	Lys	Ala	Trp	Lys	Glu		Glu	Glu

			755					760					765					
	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775	Val	Gly	Val	Ile	Gly 780	Tyr	Leu	Glu	Asp		
5	Gln 785	Ile	Met	Ser	Leu	His 790	Ala	Glu	Ile	Met	Gly 795	Leu	Gln	Lys	Ser	Pro 800		
	Tyr	Gly	Arg	Arg	Gln 805	Gly	Asp	Leu	Met	Glu 810	Ser	Leu	Glu	Gln	Arg 815	Ala		
	Ile	Asp	Leu	Tyr 820		Gln	Leu	Lys	His 825	Arg	Pro	Ser	Asp	His 830	Ser	Tyr		
10	Ser	Asp	Ser 835		Glu	Met	Val	Lys 840		Ile	Val	His	Thr 845		Gln	Ser		
	Gln	Asp 850	Arg	Val	Leu	Lys	Glu 855		Phe	Gly	His	Leu 860		Lys	Leu	Leu		
15	Gly 865		Lys	Gln	Lys	Ile 870	_	Asp	Leu	Leu	Pro 875		Val	Glu	Val	Ala 880		
13		Ser	Asn	Ile	Lys 885		Ala	Asp	Asn	Thr 890		Met	Phe	Met	Gln 895			
	Lys	Arg	Gln	_		Ile	Trp	His			Lys	Ile	Ala			Gln		
20	Ser	Ser	Ala	900 Arg	Ser	Leu	Val	_	905 Ser	Ser	Leu	Glu		910 Ala	Val	Thr		
	Pro		915 Thr	Ser	Ala	Trp		920 Pro	Pro	Thr	Ser		925 Glu	His	Asp	His		
	Ser	930 Leu	Ser	Cvs	Val	Val	935 Thr	Pro	Gln	Asp	Glv	940 Glu	Thr	Ser	Ala	Gln		
25	945			4		950				-	955					960		
	Met	Ile	Glu	Glu	Asn 965	Leu	Asn	Cys	Leu	Gly 970	His	Leu	Ser	Thr	Ile 975	Ile		
	His	Glu	Ala	Asn 980		Glu	Gln	Gly	Asn 985		Met	Met	Asn	Leu 990	Asp	Trp		
30	Ser	Trp	Leu 995	Thr	Glu													
			(2)	) IN	FORM.	ATIO	N FO	R SE	O ID	NO:	122:							
35		(	i) S1						-									
						299 ucle		~	airs									
						DNES Y: 1		_	е									
40			(-,					_										
			ii)   ix)			TYP	E: c	DNA										
45								_	eque	nce								
45						ON: INFO												
		(	xi)	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	122:						
50																GAG	4	8
	Met 1	Glu	Arg	Pro	Pro 5	GIY	Leu	Arg	Pro	Gly 10	. ATa	. СТУ	GIA	Pro	15	Glu		
55																TAC	9	6
55	Met	Arg	Glu	Arg	Leu	г СТУ	Thr	Gly	, Gly 25	Phe	: GTÀ	/ AST	ı val	. Cys 30	ь ьет	Tyr		

5				GAT Asp									144
J	_			AAC Asn									192
10				CAT His 70									240
15				TTG Leu									288
20				GAT Asp									336
25				GAA Glu									384
				TAT Tyr									432
30				ATA Ile 150									480
35				CTG Leu									528
40				GTG Val							Glu		576
45				TAC Tyr		Thr				Ser			624
				TGT Cys					Phe				672
50		Gln		TGG Trp 230	His			Lys					720
55				Glu			Glu					AGC Ser	768

5					CCA Pro												816
3					CAG Gln												864
10					CTT Leu												912
15					AAT Asn												960
20	Ala	Lys	Ile	Ile	TCT Ser 325	Phe	Leu	Leu	Pro	Pro 330	Asp	Glu	Ser	Leu	His 335	Ser	1008
25	Leu	Gln	Ser	Arg 340	ATT Ile	Glu	Arg	Glu	Thr 345	Gly	Ile	Asn	Thr	Gly 350	Ser	Gln	1056
	Glu	Leu	Leu 355	Ser	GAG Glu	Thr	Gly	11e 360	Ser	Leu	Asp	Pro	Arg 365	Lys	Pro	Ala	1104
30					CTA Leu												1152
35		Leu			AAA Lys							Gly					1200
40											Val					Ile	1248
45					Ile					Val					Val	CAC His	1296
				Gly					Tyr					Gln		CAA Gln	1344
50			Ala					Leu					Asr			A AAA Lys	1392
55		Lys					Ser					ı Lev				TTG Leu 480	1440

5		TTT Phe														1488
3		ACG Thr														1536
10		GAA Glu 515														1584
15		GAG Glu														1632
20		AGC Ser														1680
25		CGT Arg														1728
		TCC Ser														1776
30		CAG Gln 595						Leu								1824
35		TTG Leu					Gln					Leu				1872
40	Glu			Leu		Asn	Ile		Glu	Ala	Asp	Asn			ATG Met 640	1920
45					Arg					Tr					ATT	1968
.5				ser Ser					: Lev					: Lei	GAA Glu	2016
50			Thi					r Ala					Th:		A GCA Ala	2064
55		a Ası					r Cy					o Gli			G GAG y Glu	2112

5				CAA Gln													2160
-				ATT Ile													2208
10				TGG Trp 740													2256
15				GCC Ala													2304
20	Val	Val 770	Pro	ATC Ile	Leu	Val	Glu 775	Leu	Asp	Gly	Asp	Val 780	Asn	Gly	His	Lys	2352
25	Phe 785	Ser	Val	TCC Ser	Gly	Glu 790	Gly	Glu	Gly	Asp	Ala 795	Thr	Tyr	Gly	Lys	Leu 800	2400
	Thr	Leu	Lys	TTC Phe	Ile 805	Cys	Thr	Thr	Gly	Lys 810	Leu	Pro	Val	Pro	Trp 815	Pro	2448
30	Thr	Leu	Val	ACC Thr 820	Thr	Leu	Thr	Tyr	Gly 825	Val	Gln	Cys	Phe	Ser 830	Arg	Tyr	2496
35	Pro	Asp	His 835	ATG Met	Lys	Gln	His	Asp 840	Phe	Phe	Lys	Ser	Ala 845	Met	Pro	Glu	2544
40				CAG Gln													2592
45				GCC Ala													2640
				AAG Lys													2688
50				GAG Glu 900													2736
55				AAG Lys													2784

238

5		GAG Glu 930															2832
J		ATC Ile															2880
10		CAG Gln															2928
15		CTG Leu															2976
20		CTG Leu			TAA												2991
			(2)	INE	FORM	TIOI	N FOR	R SE(	O ID	NO:	L23:						
25		i)	(A) (B) (C)	EQUEN LENC TYPI STRA	E: ar ANDEI	996 mino ONES	amin acio 3: s:	no ad i ingle	cids								
30		7)	i) M	MOLEC	CULE ENT	TYPI TYPE	E: p:	rote: terna	al	a	NO.						
35	Met	Glu		SEQUI Pro									Glv	Pro	Tro	Glu	
	1				5					10					15	Tyr	
40	Gln	His	_			_		-		Ala	Ile	Lys		30 Cys	Arg	Leu	
	Glu	Leu 50	35 Ser		Lys					Trp	Cys	His 60	45 Glu	Ile	Gln	Ile	
45	Met 65	Lys	Lys	Leu	Asn	His 70	Ala	Asn	Val	Val	Lys 75	Ala	Cys	Asp	Val	Pro 80	
					85					90					95	Glu	
50	_	_		100	_	_		_	105				_	110		Asn	
50			115		_			120					125		_	Ile	
		130	_			_	135				-	140			_	Asp	
55	145		210	GIU	nou	150		пап	GIII	. Asp	155	_	GIY	nys	116	: Ile 160	
	His	Lys	Ile	Ile	Asp	Leu	Gly	Tyr	Ala	Lys	Asp	Val	Asp	Gln	Gly	Ser	

					165					170					175	
	Leu	Суѕ	Thr	Ser 180	Phe	Val	Gly	Thr	Leu 185		Tyr	Leu	Ala	Pro 190		Leu
5	Phe	Glu	Asn 195	Lys	Pro	Tyr	Thr	Ala 200	Thr	Val	qaA	Tyr	Trp 205	Ser	Phe	Gly
	Thr	Met 210	Val	Phe	Glu	Cys	Ile 215	Ala	Gly	Tyr	Arg	Pro 220	Phe	Leu	His	His
	Leu 225	Gln	Pro	Phe	Thr	Trp 230	His	Glu	Lys	Ile	Lys 235	Lys	Lys	Asp	Pro	Lys 240
10	Cys	Ile	Phe	Ala	Cys 245	Glu	Glu	Met	Ser	Gly 250	Glu	Val	Arg	Phe	Ser 255	Ser
	His	Leu	Pro	Gln 260	Pro	Asn	Ser	Leu	Cys 265	Ser	Leu	Ile	Val	Glu 270	Pro	Met
15			275					280			_		285	Gln		
		290					295					300		Val		
	305					310					315			Met		320
20					325					330				Leu	335	
				340					345	_				Gly 350		
25			355					360					365	Lys		
		370					375					380		Tyr		
20	385					390				_	395	_		Phe		400
30					405					410			-	Ser	415	
				420					425					Ala 430		
35			435					440					445	Gln		
		450					455					460		Leu		
40	465					470					475			Ala		480
40					485					490			_	Tyr	495	
				500					505					Ala 510 Val		
45			515					520					525	Met		
		530					535					540		Glu		
50	545					550					555			Arg		560
30					565					570					575	
				580					585					Ile 590 Gly		
55			595					600					605	Leu		
	Ser	באלה	⊒eu	عات ت	Сту	~ys	пλя	GTII	ьys	TTE	TTE	wab	πeπ	ьeu	PT.O	пув

240

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610
                              615
                                                   620
      Val Glu Val Ala Leu Ser Asn Ile Lys Glu Ala Asp Asn Thr Val Met
                          630
                                               635
      Phe Met Gln Gly Lys Arg Gln Lys Glu Ile Trp His Leu Leu Lys Ile
 5
                                           650
      Ala Cys Thr Gln Ser Ser Ala Arg Ser Leu Val Gly Ser Ser Leu Glu
                                       665
      Gly Ala Val Thr Pro Gln Thr Ser Ala Trp Leu Pro Pro Thr Ser Ala
                                  680
10
      Glu His Asp His Ser Leu Ser Cys Val Val Thr Pro Gln Asp Gly Glu
                              695
                                                  700
      Thr Ser Ala Gln Met Ile Glu Glu Asn Leu Asn Cys Leu Gly His Leu
                          710
                                              715
      Ser Thr Ile Ile His Glu Ala Asn Glu Glu Gln Gly Asn Ser Met Met
15
                                          730
      Asn Leu Asp Trp Ser Trp Leu Thr Glu Trp Val Pro Arg Ala Arg Asp
                  740
                                      745
      Pro Pro Val Ala Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly
                                  760
      Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys
20
      Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu
                                               795
      Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro
25
                      805
                                          810
      Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr
                                      825
      Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu
                                  840
30
      Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr
                              855
      Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg
                          870
                                               875
      Ile Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly
35
                                          890
     His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala
                                      905
      Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn
                                  920
40
      Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr
                              935
                                                  940
      Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser
                       . 950
                                              955
      Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met
45
                      965
                                          970
      Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp
                  980
     Glu Leu Tyr Lys
             995
50
```

(2) INFORMATION FOR SEQ ID NO:124:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1908 base pairs
- (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single

241

48

241

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

5 (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1905 (D) OTHER INFORMATION: 10 (xi) SEQUENCE DESCRIPTION: SEO ID NO:124: ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG

15 GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu

20 . GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35

TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC 192 25 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50

CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 30

CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu

CGC ACC ATC TTC TAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu

40 GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC 384 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly

ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 45 130 135

AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 50 145 150 155

GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170

55

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC

									•	L-72_								
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly		
5														TCC Ser	_		624	
			195					200					205			_		
10		Lys												CTG Leu			672	
10	GTG	210 ACC	GCC	GCC	GGG	ATC		CTC	GGC	ATG	GAC		CTG	TAC	AAG	TCC	720 ·	
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240		
15														GTC Val			768	
	GIY	реп	AIG	ser	245	AIA	GIII	Ald	261	250	ser	Giu	IIIL	vai	255	Mec		
20														CTT Leu			816	
	a.m	999		260	CCA	maa	<b>C</b> MC	O COTT	265	900	N 00	aam	000	270	ccc	True C	864	
25														CAG Gln			004	
														TTT Phe			912	
30		290					295					300						
25														AAC Asn			960	
35														TTC Phe			1008	
	110	•441	5	017	325	2,5	-7-		0	330					335			
40					Arg					Leu				AGC Ser 350	ГÀЗ	_	1056	
45														GAG Glu			1104	
	-		355					360					365					
50		Gly	Gly				Pro	Pro				Pro	Thr	TGG			1152	
50	ccc	370		י ככם	י ייירר	י ככם	375		י פייני	י מאס	: CNG	380		A A CIC	: CAC	CAG	1200	
		Asn					Glu					Glr				Gln 400	2200	
55			. cca	TCG	GAG			GAG	G CGC	CGG	GTC	TCC	CAA C	r gca	√ GG <i>I</i>	A GGC	1248	242

	Pro	Gly	Pro	Ser	Glu 405	His	Ile	Glu	Arg	Arg 410	Val	Ser	Asn	Ala	Gly 415	Gly	
5			GCT Ala	Pro					Pro					Gly			1296
			CCA														1344
10	Pro	Pro	Pro 435	Gly	Pro	Pro	Pro	Pro 440	Pro	Gly	Leu	Pro	Pro 445	Ser	GIA	Val	
			GCA Ala														1392
15			GCA Ala														1440
20	465					470		_		-	475		_			480	
20			GCA Ala														1488
25			GCC Ala														1536
	AGC	GGA	GGT	500 GGG	GGA	CTC	ATG	GAA	505 GAG	ATG	AAC	GCC	ATG	510 CTG	GCC	CGG	1584
30	Ser	Gly	Gly 515	Gly	Gly	Leu	Met	Glu 520	Glu	Met	Asn	Ala	Met 525	Leu	Ala	Arg	
			AAA Lys														1632
35																	
			CAG Gln														1680
	545					550					555					560	
40			AGA														1728
	vai	Arg	Arg	Pro	565	GIU	ьys	Asn	ser	570	Thr	ьeu	Pro	Arg	мес 575	гàг	
45			TCT Ser														1776
45	ser	261	261	580	vai	IIIL	1111	ser	585	1111	GIII	PIO	Сув	590		261	
50			GAT Asp 595													GAA Glu	1824
	a a a	C.T.C.		220	C2 2	mma	G		O.M.O.		an a	CNA		3 mm	(T) N	ccc	1077
<b>.</b>													Ile			GCC	1872
55	TTC	GTC	CAG	GAG	CTG	AGG	AAG	CGG	GGT	TCT	ccc	TGA					1908

244

Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro 625 630 635

- 5 (2) INFORMATION FOR SEQ ID NO:125:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 635 amino acids
    - (B) TYPE: amino acid
- 10 (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 20 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 30 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 35 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ser Glu Thr Val Ile Met 245 250 50 Ser Glu Thr Val Ile Cys Ser Ser Arg Ala Thr Val Met Leu Tyr Asp 265 Asp Gly Asn Lys Arg Trp Leu Pro Ala Gly Thr Gly Pro Gln Ala Phe 280

244

Ser Arg Val Gln Ile Tyr His Asn Pro Thr Ala Asn Ser Phe Arg Val

Val Gly Arg Lys Met Gln Pro Asp Gln Gln Val Val Ile Asn Cys Ala

295

245

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310
                                             315
     Ile Val Arg Gly Val Lys Tyr Asn Gln Ala Thr Pro Asn Phe His Gln
                                         330
     Trp Arg Asp Ala Arg Gln Val Trp Gly Leu Asn Phe Gly Ser Lys Glu
5
                 340
                                     345
     Asp Ala Ala Gln Phe Ala Ala Gly Met Ala Ser Ala Leu Glu Ala Leu
                                 360
                                                     365
     Glu Gly Gly Pro Pro Pro Pro Pro Ala Leu Pro Thr Trp Ser Val
                             375
                                                 380
10
     Pro Asn Gly Pro Ser Pro Glu Glu Val Glu Gln Gln Lys Arg Gln Gln
                         390
                                             395
     Pro Gly Pro Ser Glu His Ile Glu Arg Arg Val Ser Asn Ala Gly Gly
                                         410
     Pro Pro Ala Pro Pro Ala Gly Gly Pro Pro Pro Pro Gly Pro Pro
15
                 420
                                     425
     Pro Pro Pro Gly Pro Pro Pro Pro Gly Leu Pro Pro Ser Gly Val
                                 440
     Pro Ala Ala His Gly Ala Gly Gly Pro Pro Pro Ala Pro Pro
                             455
20
     Leu Pro Ala Ala Gln Gly Pro Gly Gly Gly Ala Gly Ala Pro Gly
                         470
                                             475
     Leu Ala Ala Ile Ala Gly Ala Lys Leu Arg Lys Val Ser Lys Gln
                     485
                                         490
     Glu Glu Ala Ser Gly Gly Pro Thr Ala Pro Lys Ala Glu Ser Gly Arg
25
                 500
                                     505
     Ser Gly Gly Gly Leu Met Glu Glu Met Asn Ala Met Leu Ala Arq
                                 520
     Arg Arg Lys Ala Thr Gln Val Gly Glu Lys Thr Pro Lys Asp Glu Ser
                             535
                                                 540
30
     Ala Asn Gln Glu Glu Pro Glu Ala Arg Val Pro Ala Gln Ser Glu Ser
                                             555
     Val Arg Arg Pro Trp Glu Lys Asn Ser Thr Thr Leu Pro Arg Met Lys
                     565
                                         570
     Ser Ser Ser Ser Val Thr Thr Ser Glu Thr Gln Pro Cys Thr Pro Ser
35
                 580
                                     585
     Ser Ser Asp Tyr Ser Asp Leu Gln Arg Val Lys Gln Glu Leu Leu Glu
                                 600
     Glu Val Lys Lys Glu Leu Gln Lys Val Lys Glu Glu Ile Ile Glu Ala
                             615
40
     Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro
     625
                         630
               (2) INFORMATION FOR SEQ ID NO:126:
45
           (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 1329 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
```

- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
  - (ix) FEATURE:
    - (A) NAME/KEY: Coding Sequence
- 55 (B) LOCATION: 1...1326
  - (D) OTHER INFORMATION:

246

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

5	ATG Met 1																48
10	GTC Val																96
15				GGC Gly											_		144
10				GGC Gly													192
20				GGC Gly													240
25				TTC Phe													288
30				TTC Phe 100													336
35				GAG Glu													384
			Phe	AAG Lys				Asn								TAC Tyr	432
40							Val					Asp				AAC Asn 160	480
45						Phe					Asn					AGC Ser	528
50					Asp					Asn					Asp	GGC Gly	576
55				Leu					туг					ser Ser		CTG Leu	624
-	AGC	AAA	A GAC	ccc	: AAC	GAG	AA E	G CGC	GAT	CAC	C ATO	GTC	CTC	G CTC	GAC	TTC	672

	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe	
5														TAC Tyr			720
10														CGG Arg			768
														TTG Leu 270			816
15	GTC Val	TTC Phe	AGC Ser 275	AAG Lys	GAC Asp	CAG Gln	TTC Phe	CCA Pro 280	GAG Glu	GTG Val	TAT Tyr	GTG Val	CCC Pro 285	ACA Thr	GTG Val	TTT Phe	B64
20	GAG Glu	AAC Asn 290	TAT Tyr	GTG Val	GCA Ala	GAT Asp	ATC Ile 295	GAG Glu	GTG Val	GAT Asp	GGA Gly	AAG Lys 300	CAG Gln	GTA Val	GAG Glu	TTG Leu	912
25	GCT Ala 305	TTG Leu	TGG Trp	GAC Asp	ACA Thr	GCT Ala 310	GGG Gly	CAG Gln	GAA Glu	GAT Asp	TAT Tyr 315	GAT Asp	CGC Arg	CTG Leu	AGG Arg	CCC Pro 320	960
30	CTC Leu	TCC Ser	TAC Tyr	CCA Pro	GAT Asp 325	ACC Thr	GAT Asp	GTT Val	ATA Ile	CTG Leu 330	ATG Met	TGT Cys	TTT Phe	TCC Ser	ATC Ile 335	GAC Asp	1008
					Leu					Glu				CCA Pro 350			1056
35				Cys					Ile					AAT Asn			1104
40	GAT Asp	CTT Leu	Arg	AAT Asn	GAT Asp	GAG	CAC His	Thr	AGG Arg	CGG Arg	GAG Glu	CTA Leu 380	ı Ala	: AAG Lys	ATG Met	AAG Lys	1152
45		Glu					Glu					Met				ATT J lle 400	1200
50						: Met					Lys					A GTG / Val	1248
					e Glu					g Ala					a Arg	A CGT g Arg	1296
55	GGG	AA E	G AA	AA A	A TC	r GG	r TG	C CT	r gr	C TT	G TG	A					1329 247

248

Gly Lys Lys Ser Gly Cys Leu Val Leu 435 440

- 5 (2) INFORMATION FOR SEQ ID NO:127:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 442 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

15

10

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:
- Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 55 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 75 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 30 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 35 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170 40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 205 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 215 220 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ala Ala Ile Arg Lys Lys 245 250 50 Leu Val Ile Val Gly Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu Ile 265 Val Phe Ser Lys Asp Gln Phe Pro Glu Val Tyr Val Pro Thr Val Phe 280 Glu Asn Tyr Val Ala Asp Ile Glu Val Asp Gly Lys Gln Val Glu Leu 55 295 300

248

Ala Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg Pro

	305					310					315					320		
		Ser	Tyr	Pro	Asp		Asp	Val	Ile	Leu		Cvs	Phe	Ser	Ile			
			-		325		-			330		-			335	-		
5	Ser	Pro	Asp	Ser 340	Leu	Glu	Asn	Ile	Pro 345	Glu	Lys	Trp	Thr	Pro 350	Glu	Val		
	Lys	His	Phe 355	Cys	Pro	Asn	Val	Pro 360	Ile	Ile	Leu	Val	Gly 365	Asn	Lys	Lys		
	Asp	Leu 370	Arg	Asn	Asp	Glu	His 375	Thr	Arg	Arg	Glu	Leu 380	Ala	Lys	Met	Lys		
10	Gln 385		Pro	Val	Lys	Pro 390		Glu	Gly	Arg	Asp 395		Ala	Asn	Arg	Ile 400		
		Ala	Phe	Gly	Tyr 405		Glu	Cys	Ser	Ala 410		Thr	Lys	Asp	Gly 415			
15	Arg	Glu	Val	Phe 420		Met	Ala	Thr	Arg 425		Ala	Leu	Gln	Ala 430		Arg		
	Gly	Lys	Lys 435		Ser	Gly	Cys	Leu 440	Val	Leu				150				
	(2) INFORMATION FOR SEQ ID NO:128:																	
20			(2)	1141	CICIAL	41101	v FOI	COE	2, 117	NO:	120:							
		( j		EQUEN LENC														
				TYPE					_									
25				TOPO				_	2									
	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:																	
30									eque	ıce								
	(B) LOCATION: 11137 (D) OTHER INFORMATION:																	
35		()	ci) s	SEQUI	ENCE	DESC	CRIP	rion	: SE	O ID	NO:	128:						
									ACC								48	
	Met 1	Asp	His	Tyr	Asp 5	Ser	Gln	Gln	Thr	Asn 10	Asp	Tyr	Met	Gln	Pro 15	Glu		
40	_								CTG								96	
	GIU	Asp	пр	20	Arg	Asp	Leu	Leu	Leu 25	Asp	Pro	Ala	Trp	30	гÀг	GIN		
	CAG	AGA	AAG	ACA	TTC	ACG	GCA	TGG	TGT	AAC	TCC	CAC	CTC	CGG	AAG	GCG	144	
45	Gln	Arg	Lys 35	Thr	Phe	Thr	Ala	Trp	Cys	Asn	Ser	His	Leu 45	Arg	Lys	Ala		
	GGG	ACA		ATC	GAG	ልልሮ	ልጥሮ		GAG	GAC	ጥጥር	ccc		GGC	ርጥር	AAC	192	
<b>F</b> 0		Thr					Ile		Glu								192	
50		50					55					60						
				CTG													240	
									TCA Ser								240	
55	Leu 65	Met	Leu	Leu	Leu	Glu 70	Val	Ile		Gly	Glu 75	Arg	Leu	Ala	Lys	Pro 80	240	

										_00								
	Glu	Arg	Gly	Lys	Met 85	Arg	Val	His	Lys	Ile 90	Ser	Asn	Val .		Lys 95	Ala		
5			TTC Phe										Ser				336	
10			ATC Ile 115														384	
15			ATC Ile														432	
15	GGC Gly 145	GAG Glu	GAG Glu	CTG Leu	TTC Phe	ACC Thr 150	GGG Gly	GTG Val	GTG Val	CCC Pro	ATC Ile 155	CTG Leu	GTC Val	GAG Glu	CTG Leu	GAC Asp 160	480	
20			GTA Val														528	
25			ACC Thr														576	
30			CCC Pro 195						Leu								624	
			TGC Cys										Gln				672	
35		Lys	TCC Ser				Glu					Glu					720	
40			GAC Asp			Asn					Ala					Glu	768	
45					ı Val					ı Let					Phe	AAG Lys	816	
50				/ Asi					5 Lys					туз		C AGC n Ser	864	
			n Val					a As					n Gly			G GTG s Val	912	
55	AA	C TT	C AA	G AT	C CG	C CA	C AA	C AT	C GA	G GA	C GG	C AG	C GT	G CA	G CT	C GCC	960	250

251

										251							
	Asn 305	Phe	Lys	Ile	Arg	His 310	Asn	Ile	Glu	Asp	Gly 315	Ser	Val	Gln	Leu	Ala 320	
5		CAC His															1008
10		GAC Asp															1056
15		GAG Glu															1104
13		ATC Ile 370										TAA					1140
20			(2)														
25		<b>( )</b>	(A) (B) (C)	EQUEN LENC TYPI STRA	FORMA  NCE (  STH:  E: ar  ANDEI  OLOGY	CHARA 379 nino ONESS	ACTEI amin acio	RISTI no ac i ingle	CS:	NO:	129:						
30		(\	/) FF	RAGMI	CULE ENT T ENCE	YPE	int	terna	al	O ID	NO:3	129:					
35	1	Asp Asp	His	туг	Asp 5	Ser	Gln	Gln	Thr	Asn 10	Asp	Tyr			15		
		Arg		20					25					30			
40	Gly	Thr	35 Gln	Ile	Glu	Asn		40 Glu	Glu	Asp	Phe		45 Asp	Gly	Leu	Lys	
	Leu 65	50 Met	Leu	Leu	Leu	Glu 70	55 Val	Ile	Ser	Gly	Glu 75	60 Arg	Leu	Ala	Lys	Pro 80	
45		Arg	Gly	Lys	Met 85		Val	His	Lys	Ile 90		Asn	Val	Asn	Lys 95		
		Asp		100			_	-	105	-				110	•		
50		Glu	115					120					125			_	
00		Ile 130 Glu					135					140					
	145			=-	-	150	-1				155				~~	160	
55	Gly	Asp	Val	Asn	Gly 165	His	Гуs	Phe	Ser	Val 170		Gly	Glu	Gly	Glu 175	Gly	
	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	

				180					185					190				
	Lys	Leu	Pro 195	Val	Pro	Trp	Pro	Thr 200	Leu	Val	Thr	Thr	Leu 205	Thr	Tyr	Gly		
5	Val	Gln 210		Phe	Ser	Arg	Tyr 215		Asp	His	Met	Lys 220		His	Asp	Phe		
		ГÀг	Ser	Ala	Met		Glu	Gly	Tyr	Val		Glu	Arg	Thr	Ile			
	225 Phe	Lys	Asp	Asp	Gly	230 Asn	Tyr	Lys	Thr	Arg	235 Ala	Glu	Val	Lys	Phe	240 Glu		
10	<b>01</b>	<b>3</b>	ml	<b>T</b>	245	<b>7</b>		~1.	<b>~</b> 1	250	<b>-</b>	<b>01</b>			255	•		
10	GIY	Asp	THE	ьец 260	vaı	Asn	Arg	TTE	265	Leu	гуз	Gly	шe	270	Pne	гуз		
	Glu	Asp	Gly 275	Asn	Ile	Leu	Gly	His 280	Lys	Leu	Glu	Tyr	Asn 285	Tyr	Asn	Ser		
15	His	Asn 290	Val	Tyr	Ile	Met	Ala 295	Asp	Lys	Gln	Lys	Asn 300	Gly	Ile	Lys	Val		
13			Lys	Ile	Arg			Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala		
	305 Asp	His	Tvr	Gln	Gln	310 Asn	Thr	Pro	Tle	Glv	315 Asp	Gly	Pro	Val	Leu	320 Leu		
	пор		-7-	0111	325	71011	****	110		330	пор	Cly	110	Val	335	Deu		
20	Pro	Asp	Asn	His	Tyr	Leu	Ser	Thr	Gln 345	Ser	Ala	Leu	Ser	Lys 350	Asp	Pro		
	Asn	Glu	Lys		Asp	His	Met	Val		Leu	Glu	Phe	Val		Ala	Ala		
	Glv	Tle	355 Thr	Len	Glv	Met	Δen	360 Glu	ī.en	ጥኒታታ	Lve		365					
25	CLY	370	****	Бси	Cly		375	010	пси	- 7 -	ДуЗ							
			(2)	TNI	TOPM:	ል <b>ጥፐ</b> በ	v EO	R SE(	ת ד	NO ·	130.							
			(2.	1141	· OKIL	11101	. 10.	•••	2 10	NO	150.							
30		( i		-				RIST: se pa										
00				TYPE				_	<b>X 1 1 1 3</b>									
				STRA				ingle r	9							•		
			(2)	1010	J1100		cu	_										
35				MOLE( FEAT		TYP	E: c	DNA										
				<b>D</b> 111.	JILL .													
				) NAI ) LO				ng S	eque	nce								
40				OTI														
		1-	ri) :	SEOII	ENCE	DES	מ ז מי	TION	. CF	O TD	NO.	130.						
		(,	,	3 <u>D</u> Q01	DIVC L	יטמט	CICLE	TION	. 55	Q ID	NO.	150.						
45												GTG Val					4 8	3
70	1	vai	361	цуъ	5	Giu	GIU	Deu	PILE	10	Gly	vaı	Val	PIO	15	пец		
	GTC	CAG	CTC	GNC	GGG	G N C	CTTA	አክሮ	ccc	CAC	አ አ <del>ረ</del>	TTC	אכיכי	CTC	TOO	ccc	9	<b>s</b>
												Phe					,	J
50				20					25					30				
	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	14	4
	Glu	Gly		Gly	Asp	Ala	Thr	_	Gly	Lys	Leu	Thr		Lys	Phe	Ile		
55			35					40					45					
	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC	ACC	19	
																		252

	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
5				GGC Gly													240
10				TTC Phe													288
				TTC Phe 100													336
15				GAG Glu													384
20.				AAG Lys													432
25				AGC Ser												AAC Asn 160	480
30				GTG Val													528
					Asp											GGC Gly	576
35				Leu					Tyr					Ser		CTG Leu	624
40			Asp					Arg					. Leu			TTC Phe	672
45		Thr					Thr					Gli				TCC Ser 240	720
50						g Ala					Glu					A CCC n Pro	768
					Ala					ı Pro					Gli	A GAC n Asp	816
55	GAC	G CT	r gao	C TTO	C TC	TA C	CT(	TT(	C GA	C TA	r gao	TA	T TT	G AA	CC	G AAC	864 253

	Glu	Leu	Asp 275	Phe	Ser	Ile	Leu	Phe 280	Asp	Tyr	Glu	Tyr	Leu 285	Asn	Pro	Asn		
5											AGC Ser						912	
10											CTC Leu 315						960	
	-										CGA Arg						1008	
15											GCC Ala					_	1056	
20											CCG Pro					_	1104	
25											GCG Ala				_		1152	
30											CCG Pro 395						1200	
						Gly					CTT Leu						1248	
35											GAC Asp						1296	
40				Cys							GGG Gly						1344	
45			Phe					Ala					Arg			CCA Pro	1392	
50		Met					Ser					Ser				CGC Arg 480	1440	
	-					Arg					Ser					GCC Ala	1488	
55	DAA	CGC	G AGG	CAT	TCG	TGC	: GCC	GAG	GCC	TTG	GTI	GC(	CTC	CCG	CCC	: GGA	1536	254

	Lys	Arg	Arg	His 500	Ser	Cys	Ala	Glu	Ala 505	Leu	Val	Ala	Leu	Pro 510	Pro	Gly	
5									CCC Pro								1584
10									CCG Pro								1632
4.5									CTG Leu								1680
15									TGG Trp								1728
20									GCC Ala 585								1776
25									TGC Cys								1824
30									GTT Val								1872
									AGC Ser								1920
35									AGT Ser								1968
40									CAT His 665	_	-			_			2016
45									GCT Ala								2064
50									AAC Asn								2112
									ATC Ile								2160
55	CAG	GTG	CAC	CGA	ATC	ACG	GGG	AAA	ACT	GTC	ACC	ACC	ACC	AGC	TAT	GAG	2208

									•	256								
	Gln	Val	His	Arg	Ile 725	Thr	Gly	Lys	Thr	Val 730	Thr	Thr	Thr	Ser	Tyr 735	Glu		
5			GTG Val														2256	
10			ATG Met 755														2304	
			GAC Asp														2352	
15			CGG Arg														2400	
20			ATC Ile														2448	
25			TCT Ser														2496	
30			CTG Leu 835														2544	
25			TCC										Thr				2592	
35		Gln	ATT				Glu					Lys					2640	
40			ATG Met			Val										Ile	2688	
45					Lys					Val					Arg	AAA Lys	2736	
50				Pro					туг					Ala		AAG Lys	2784	
			ı Pro					Asp					e Cys			C ACC Thr	2832	
55	CAT	r GG <i>I</i>	A GGC	CTC	GG(	AGC	CAC	GCT	TAC	TAC	CC(	C CA	G CAC	CCC	TA E	GTG	2880	256

	His 945	Gly	Gly	Leu	Gly	Ser 950	Gln	Pro	Tyr	Tyr	Pro 955	Gln	His	Pro	Met	Val 960		
	GCC	GAG	<b>יירר</b>	כככ	TCC		CTC	GTG	GCC	אככ		CCT	CCC	TCC	C A C	_	2928	
5					Ser												2926	
					965	- 4				970				-, -	975	02		
	mmc.	000	7.00	000	ama	mar	<b></b>			~~~								
					CTC Leu												2976	
10				980	LCu	.UCI	ber	FIO	985	AIG	AIG	ıyı	GIII	990	GIII	ASII		
					CTC												3024	
	PIO	Ala	995	vaı	Leu	Tyr		Arg 1000	Ser	гуs	Ser		Ser 1005	Pro	Ser	Leu		
15			,,,				_	1000				-	1003					
					CAG												3072	
			Tyr	Gln	Gln			Leu	Met	Ala			Leu	Ser	Leu	Ala		
		1010				3	1015				]	1020						
20	GAC	GCT	CAC	CGC	TCT	GTG	CTG	GTG	CAC	GCC	GGC	TCC	CAG	GGC	CAG	AGC	3120	
	Asp				Ser													
	1025				=	L030				-	1035				]	1040		
	TCA	GCC	CTG	CTC	CAC	ccc	TCT	CCG	ACC	AAC	CAG	CAG	GCC	TCG	ССТ	GTG	3168	
25					His												3200	
				1	1045					1050				=	1055			
	ATC	CAC	TAC	TCA	ccc	ACC	אאכי	CAG	CAG	ርሞር	רפר	ጥርር	GGA	AGC	CAC	ሮልር	3216	
					Pro												3210	
30				1060					1065		_	-	-	1070				
	GNG	ጥጥር	כאכ	CNC	ATC	<b>አ</b> ሞር	ma a	maa	O N C	2211	mmo	CCN	001	000	200	7.00	2264	
					Ile												3264	
			1075					1080		•••			1085	Q1 <i>y</i>		1111		
35	3.53	aam																
					CCC Pro												3312	
		1090	Oly	FLO	FIO		1095	ser	GIII	СТУ		1100	пец	ser	PIO	GIY		
40					GTC												3360	
	1105	Tyr	Pro	Thr	Val	1110	Gin	Gin	GIn		Ala 1115	Thr	Ser	Gin		Ala 1120		
	-100				•					•					-	1120		
					CCC												3408	
45	Ala	Lys	Asn		Pro	Pro	Val	Ser			Lys	Glu	Val			Ala		
					1125				•	1130					1135			
	GGG	GTG	ACC	ATT	AAA	CAG	GAG	CAG	AAC	TTG	GAC	CAG	ACC	TAC	TTG	GAT	3456	
<b>r</b> 0	Gly	Val			ГÀг	Gln	Glu			Leu	Asp	Gln	Thr	Tyr	Leu	Asp		
50				1140				:	1145				:	1150				
	GAT	GTT	AAT	GAA	ATT	ATC	AGG	AAG	GAG	TTT	TCA	GGA	ССТ	CCT	GCC	AGA	3504	
					Ile													
55			1155				:	1160				;	1165					
JJ	ААТ	CAG	ACG	TAA													3516	
																	257	

258

Asn Gln Thr 1170

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5
               (2) INFORMATION FOR SEQ ID NO:131:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 1171 amino acids
              (B) TYPE: amino acid
10
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
15
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:
      Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
20
      Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
                                      25
      Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
      Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
25
                              55
                                                  60
      Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                          70
                                              75
      Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
30
      Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
                                      105
      Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                  120
      Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
35
                              135
      Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                          150
                                               155
      Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                                           170
40
      Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
                                      185
                                                           190
                  180
      Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
                                                       205
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
45
                              215
                                                   220
      Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                           230
      Gly Leu Arg Ser Arg Ala Met Asn Ala Pro Glu Arg Gln Pro Gln Pro
                      245
                                           250
50
      Asp Gly Gly Asp Ala Pro Gly His Glu Pro Gly Gly Ser Pro Gln Asp
                                       265
      Glu Leu Asp Phe Ser Ile Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn
                                   280
      Glu Glu Glu Pro Asn Ala His Lys Val Ala Ser Pro Pro Ser Gly Pro
55
                               295
                                                   300
      Ala Tyr Pro Asp Asp Val Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro
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	305					310					315					320
		Ala	Ser	Leu	Ser		Glu	Pro	Pro	Gly		Phe	Glv	Glu	Pro	_
					325	•				330	5		2		335	E
-	Arg	Val	Gly		Gln	Lys	Phe	Leu		Ala	Ala	Lys	Pro	Ala	Gly	Ala
5	C	03	T	340	<b>D</b>		<b>-</b> 7 -	~7	345		_	_		350	_	
	ser	GIY	ьеu 355	ser	Pro	Arg	TIE	360	11e	Thr	Pro	Ser	H15	GIu	Leu	IIe
	Gln	Ala	Val	Gly	Pro	Leu	Arg		Arg	Asp	Ala	Gly	_	Leu	Val	Glu
		370					375			_		380				
10		Pro	Pro	Leu	Ala		Val	Ala	Ala	Ser		Arg	Phe	Thr	Leu	
	385 Val	Dro	Glaz	Dhe	G1.,	390	Th 22	7) 200	~1	Pro	395	0	T 0	C	7	400
	vaı	FIO	GIY	FIIC	405	GIY	ıyı	мгg	GIU	410	Leu	Cys	пеп	ser	415	AIG
	Ser	Ser	Gly	Ser	Ser	Ala	Ser	Phe	Ile	Ser	Asp	Thr	Phe	Ser	Pro	Tyr
15				420					425					430		
	Thr	Ser		Cys	Val	Ser	Pro		Asn	Gly	Gly	Pro		Asp	Leu	Cys
	Pro	Gln	435 Phe	Gln	Δen	Tle	Dro	440 Ala	น่า	Tyr	Car	Dro	445	Th.∽	Cor	Dro
		450				-10	455			- 7 -	DCI	460	my	1111	DCI	FIO
20	Ile	Met	Ser	Pro	Arg	Thr	Ser	Leu	Ala	Glu	Asp	Ser	Cys	Leu	Gly	Arg
	465					470		_			475					480
	His	Ser	Pro	Val	Pro 485	Arg	Pro	Ala	Ser	Arg 490	Ser	Ser	Ser	Pro	Gly 495	Ala
	Lys	Arq	Arq	His		Cvs	Ala	Glu	Ala	Leu	Val	Ala	Leu	Pro	_	Glv
25	•		_	500		- 4			505					510		1
	Ala	Ser		Gln	Arg	Ser	Arg	Ser	Pro	Ser	Pro	${\tt Gln}$	Pro	Ser	Ser	His
	77- 7		515	~ 7	_			520	_			_	525	_		
	vaı	530	Pro	Gin	Asp	His	232 232	Ser	Pro	Ala	GIA	Tyr 540	Pro	Pro	Val	Ala
30	Gly		Ala	Val	Ile	Met		Ala	Leu	Asn	Ser		Ala	Thr	Asp	Ser
	545					550	•				555				<u>F</u> -	560
	Pro	Cys	Gly	Ile		Pro	Lys	Met	$\mathtt{Trp}$	Lys	Thr	Ser	Pro	Asp	Pro	Ser
	D~0	11-7	Com	7.1.	565	D		<b>T</b>	n 1 -	570		<b>.</b>		<b></b>	575	<b></b> .
35	PLO	vaı	ser	580	Ala	PIO	ser	ьys	585	Gly	Leu	Pro	Arg	H15	iie	Tyr
	Pro	Ala	Val		Phe	Leu	Gly	Pro		Glu	Gln	Gly	Glu		Arg	Asn
			595					600					605			
	Ser		Pro	Glu	Ser	Ile		Leu	Val	Pro	Pro		$\mathtt{Trp}$	Pro	Lys	Pro
40	ī.eu	610 Val	Dro	תות	Tla	Dro	615	Crea	Cox	Ile	D	620	(T) base	77-	C	T
-10	625	Vai	FIO	міа	116	630	116	Cys	ser	TIE	635	val	int	Ald	Ser	640
		Pro	Leu	Glu	Trp		Leu	Ser	Ser	Gln		Gly	Ser	Tyr	Glu	
					645					650		_		_	655	
45	Arg	Ile	Glu		Gln	Pro	Lys	Pro		His	Arg	Ala	His	_	Glu	Thr
45	Glu	Gly	802	660	C111	ח ז ת	77-7	T 1.00	665	Dwa	mla sa	<b>a</b> 1	a1	670	D	37-3
	Giu	GIY	675	Arg	GIA	Ата	vaı	680	ALA	Pro	THE	GTÀ	685	HIS	PIO	val
	Val	Gln		His	Gly	Tyr	Met		Asn	Lys	Pro	Leu		Leu	Gln	Ile
		690					695					700				
50		Ile	Gly	Thr	Ala		Glu	Arg	Ile	Leu		Pro	His	Ala	Phe	
	705	Wa I	uia	7 ~~~	710	710	<b>03</b>	T	ml	37m ]	715	mb	(T)	0	m	720
	0111	val	1172	~r.a	725	TIIL	GIĀ	пÀя	THE	Val 730	THE	THE	TUL	ser	735	GIU
	Lys	Ile	Val	Gly		Thr	Lys	Val	Leu	Glu	Ile	Pro	Leu	Glu		Lys
55				740					745					750		_
	Asn	Asn	Met	Arg	Ala	Thr	Ile	Asp	Cys	Ala	Gly	Ile	Leu	Lys	Leu	Arg

260

			755					760					765			
	Asn	Ala 770	Asp	Ile	Glu	Leu	Arg 775	Lys	Gly	Glu	Thr	Asp 780	Ile	Gly	Arg	Lys
5	Asn 785	Thr	Arg	Val	Arg	Leu 790	Val	Phe	Arg	Val	His 795	Ile	Pro	Glu	Ser	Ser 800
	Gly	Arg	Ile	Val	Ser 805	Leu	Gln	Thr	Ala	Ser 810	Asn	Pro	Ile	Glu	Cys 815	Ser
	Gln	Arg	Ser	Ala 820	His	Glu	Leu	Pro	Met 825	Val	Glu	Arg	Gln	Asp 830	Thr	Asp
10	Ser	Cys	Leu 835	Val	Tyr	Gly	Gly	Gln 840	Gln	Met	Ile	Leu	Thr 845	Gly	Gln	Asn
	Phe	Thr 850	Ser	Glu	Ser	Lys	Val 855	Val	Phe	Thr	Glu	Lys 860	Thr	Thr	Asp	Gly
15	Gln 865	Gln	Ile	Trp	Glu	Met 870	Glu	Ala	Thr	Val	Asp 875	Lys	Asp	Lys	Ser	Gln 880
	Pro	Asn	Met	Leu	Phe 885	Val	Glu	Ile	Pro	Glu 890	Tyr	Arg	Asn	Lys	His 895	Ile
	Arg	Thr	Pro	Val 900	Lys	Val	Asn	Phe	Tyr 905	Val	Ile	Asn	Gly	Lys 910	Arg	Lys
20	Arg	Ser	Gln 915	Pro	Gln	His	Phe	Thr 920	Tyr	His	Pro	Val	Pro 925	Ala	Ile	Lys
		930			Asp		935	_				940				
25	His 945	Gly	Gly	Leu	Gly	Ser 950	Gln	Pro	Tyr	Tyr	Pro 955	Gln	His	Pro	Met	Val 960
20		Glu	Ser	Pro	Ser 965		Leu	Val	Ala	Thr 970		Ala	Pro	Cys	Gln 975	
	Phe	Arg	Thr	Gly 980	Leu	Ser	Ser	Pro	Asp 985		Arg	Tyr	Gln	Gln 990	Gln	Asn
30	Pro	Ala	Ala 995	Val	Leu	Tyr		Arg 1000	Ser	Lys	Ser		Ser 1005	Pro	Ser	Leu
		Gly 1010	Tyr	Gln	Gln		Ala 1015	Leu	Met	Ala		Pro 1020		Ser	Leu	Ala
35	Asp 025	Ala	His	Arg	Ser	Val 1030		Val	His		Gly 1035		Gln	Gly		Ser 1040
		Ala	Leu		His 1045			Pro			Gln		Ala		Pro 1055	
	Ile	His			Pro	Thr	Asn			Leu		Cys		Ser 1070		Gln
40	Glu		Gln 1075		Ile	Met		Cys 1080		Asn	Phe		Pro		Thr	Thr
	_	Pro 1090	_	Pro	Pro	Pro	Val 1095		Gln	Gly	Gln	Arg		Ser	Pro	Gly
A.E.		_	Pro	Thr	Val			Gln	Gln	Asn			Ser	Gln	Arg	
45	105 Ala		Asn	Glv	Pro	1110 Pro		Ser	Asc	Gln	1115 Lvs		. Val	. Lev	Pro	1120 Ala
					1125					1130	)				1135	;
				1140					1145	5				1150	· ·	
50	Asp	Val	. Asn 1155		ılle	: Ile	e Arg	1160		ı Phe	e Ser	Gly	Pro 1165		Ala	a Arg
	Asn	Glr 1170	Thr													

(2) INFORMATION FOR SEQ ID NO:132:

5		(:	(A) (B) (C) (D) ii) 1 ix) 1	LENG TYP: STR. TOPG MOLEG FEATS	GTH: E: no ANDE OLOG CULE URE:	3540 ucle: DNES: Y: 1: TYPD	ACTE 6 bas ic ac S: s: inea: E: cl	se pacid ingle r ONA	airs e	nce								
			(D)	OT:	HER :	INFO	RMAT	ON:										
15		(2	xi) :	SEQU	ENCE	DES	CRIP	rion	: SE	Q ID	NO:	132:						
.0	ATG AAC GCC CCC GAG CGG CAG CCC CAA CCC GAC GGC GG																	
20	GGC Gly	CAC His	GAG Glu	Pro	GGG Gly	GGC Gly	AGC Ser	CCC Pro	Gln	GAC Asp	GAG Glu	CTT Leu	GAC Asp	Phe	TCC Ser	ATC Ile	96	
25		TTC Phe															144	
30	CAT His	AAG Lys 50	GTC Val	GCC Ala	AGC Ser	CCA Pro	CCC Pro 55	TCC Ser	GGA Gly	CCC Pro	GCA Ala	TAC Tyr 60	CCC Pro	GAT Asp	GAT Asp	GTA Val	192	
35		GAC Asp															240	
	GAG Glu	CCC Pro	CCC Pro	GGC Gly	CGA Arg 85	TTC Phe	GGA Gly	GAG Glu	CCG Pro	GAT Asp 90	AGG Arg	GTA Val	GGG Gly	CCG Pro	CAG Gln 95	AAG Lys	288	
40	TTT Phe	CTG Leu	AGC Ser	GCG Ala 100	GCC Ala	AAG Lys	CCA Pro	GCA Ala	GGG Gly 105	GCC Ala	TCG Ser	GGC Gly	CTG Leu	AGC Ser 110	CCT Pro	CGG Arg	336	
45	ATC Ile	GAG Glu	ATC Ile 115	ACT Thr	CCG Pro	TCC Ser	CAC His	GAA Glu 120	CTG Leu	ATC Ile	CAG Gln	GCA Ala	GTG Val 125	GGG Gly	CCC Pro	CTC Leu	384	
50		ATG Met 130															432	
55	GTG Val 145	GCC Ala	GCC Ala	AGC Ser	CCG Pro	AGG Arg 150	TTC Phe	ACC Thr	CTG Leu	CCC Pro	GTG Val 155	CCC Pro	GGC Gly	TTC Phe	GAG Glu	GGC Gly 160	480	
	TAC	CGC	GAG	CCG	CTT	TGC	TTG	AGC	ccc	GCT	AGC	AGC	GGC	TCC	TCT	GCC	528	261

262

	Tyr	Arg	Glu	Pro	Leu 165	Cys	Leu	Ser	Pro	Ala 170	Ser	Ser	Gly	Ser	Ser 175	Ala	
5														TGC Cys 190			576
10														CAA Gln			624
45														CCT Pro			672
15														GTG Val			720
20														CAT His			768
25														CAG Gln 270			816
30														CAG Gln			864
25														GTG Val			912
35												Cys		ATC Ile		CCC Pro 320	960
40						Ser					Pro					CCA Pro	1008
45					Leu					Tyr					Phe	CTG Leu	1056
50			_	Glu					Arg					Glu		ATC Ile	1104
			Val					Pro					Pro			CCC Pro	1152
55	ATC	TGC	. AGC	CATO	CC#	A GTG	ACT	GCI	A TCC	C CTC	c cc	r cci	A CTT	GAC	G TGC	G CCG	1200

										203							
	Ile 385	Cys	Ser	Ile	Pro	Val 390	Thr	Ala	Ser	Leu	Pro 395	Pro	Leu	Glu	Trp	Pro 400	
5					TCA Ser 405												1248
10					CGG Arg												1296
15					ACT Thr												1344
15					CCT Pro												1392
20					AAG Lys												1440
25					ACC Thr 485												1488
30					ATC Ile												1536
35					GGG Gly												1584
33					ACG Thr												1632
40					CAC His												1680
45					AAC Asn 565												1728
50					GAA Glu												1776
55					ATC Ile												1824
JJ	GTT	GTG	TTT	ACT	GAG	AAG	ACC	ACA	GAT	GGA	CAG	CAA	ATT	TGG	GAG	ATG	1872

264

									-	2 <del>04</del>							
	Val	Val 610	Phe	Thr	Glu	Lys	Thr 615	Thr	Asp	Gly	Gln	Gln 620	Ile	Trp	Glu	Met	
5						AAG Lys 630											1920
10						CGG Arg											1968
15						AAT Asn									_	_	2016
15						GTC Val											2064
20						ATC Ile											2112
25						CAG Gln 710											2160
30						GCT Ala											2208
25						TAC Tyr											2256
35				Lys		CTG Leu			Ser								2304
40						CCG Pro		Ser									2352
45		Val				TCC Ser 790						Ala					2400
50						CAG Gln		-			Ile					Thr	2448
					Arg	TGC Cys				Gln					$Il\epsilon$		2496
55	TAC	TGC	GAC	TAA 3	TTC	: GCA	CCA	. GGC	. ACC	ACC	: AGA	CCT	GGC	cce	GCC	CCG	2544

										265							
	Tyr	Cys	Glu 835	Asn	Phe	Ala	Pro	Gly 840	Thr	Thr	Arg	Pro	Gly 845	Pro	Pro	Pro	
5									CCG Pro	-					_	_	25 <b>92</b>
10									AGA Arg								2640
15				-					CCT Pro								2688
10									TTG Leu 905							_	2736
20									GCC Ala								2784
25					-				GAT Asp			-				_	2832
30									GGG Gly								2880
35									AAG Lys								2928
33									CTG Leu 985								2976
40							Pro		CCC Pro					Thr			3024
45			Val			Phe		Arg	TAC				Met		_		3072
50		Phe					Met					. Val				ACC Thr 1040	3120
<b></b>						Asp					Thi					AAG Lys	3168
55	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	: ATC	GAC	G CTC	AAC	G GGC	ATC	C GAC	3216

266

	Phe Glu	Gly Asp		Val As	n Arg 1065	Ile Glu	Leu Lys	Gly Ile 1070	e Asp	
5	Phe Lys				u Gly		CTG GAG Leu Glu 1085	Tyr Ası		3264
10							CAG AAG Gln Lys 1100			3312
				Arg Hi			GAC GGC Asp Gly			3360
15					n Thr		GGC GAC		o Val	3408
20			Asn Hi				TCC GCC			3456
25	Asp Pro				is Met		G CTG GAC Leu Glu 1165	Phe Va		3504
30							TAC AAC 1 Tyr Lys 1180			3546
		(2) I	NFORMATI	ON FOR S	SEQ ID	NO:133	:			
35	(	(A) LE (B) TY (C) ST	ENCE CHA NGTH: 11 PE: amin RANDEDNE	81 amino o acid SS: sino	o acid:	s				
40		ii) MOL	POLOGY: ECULE TY MENT TYP	PE: pro						
45	(	xi) SEQ	UENCE DE	SCRIPTIO	ON: SE	Q ID NO	:133:			
	1		5	_		10	p Gly Gl	15	5	
50		20			25		u Leu As u Glu Gl	30		
30		35		4	0		45 a Tyr Pr			
55	50 Met Asp 65	Tyr Gl	y Leu Ly 70		yr Ser	Pro Le	60 u Ala Se	r Leu S	er Gly 80	
		Pro Gl			slu Pro		g Val Gl	y Pro G		

**\***\*

					85					90					95	
	Phe	Leu	Ser	Ala 100	. –	Lys	Pro	Ala	Gly 105		Ser	Gly	Leu	Ser 110		Arg
5	Ile	Glu	Ile 115	Thr	Pro	Ser	His	Glu 120		Ile	Gln	Ala	Val 125	Gly	Pro	Leu
	Arg	Met 130	Arg	Asp	Ala	Gly	Leu 135	Leu	Val	Glu	Gln	Pro 140	Pro	Leu	Ala	Gly
	Val 145	Ala	Ala	Ser	Pro	Arg 150	Phe	Thr	Leu	Pro	Val 155	Pro	Gly	Phe	Glu	Gly 160
10	Tyr	Arg	Glu	Pro	Leu 165	Cys	Leu	Ser	Pro	Ala 170	Ser	Ser	Gly	Ser	Ser 175	Ala
				180					185					Cys 190		
15			195					200					205	Gln		
		210					215					220		Pro		
	225					230					235			Val		240
20					245					250				His	255	
				260					265					Gln 270		
25			275					280					285	Gln		
		290					295					300		Val		
30	305					310					315			Ile		320
30					325					330				Ala	335	
				340					345					Glu 350		
35			355					360					365	Glu		
		370					375					380		Ala		
40	385					390					395			Glu Val		400
40					405					410				Arg	415	
				420					425					430 His	_	
45			435					440					445	Thr	_	_
		450					455					460		Arg		
50	465					470					475			Gly		480
					485					490				Arg	495	
				500					505					510 Ile		
55			515					520					525	Val		
		2 -	- 4					1	5	د ر ـ			9	v a 1	AL 9	TI C C

	**- 3	530	<b>3</b>	17	***	т1 _	535	<b>a</b> 1	0	G	<b>a</b> 1	540	T1.	17a 1	C ~ ~	T 011
		Pue	Arg	val	HIS		Pro	Glu	ser	ser	-	Arg	тте	var	ser	560
	545	mb	77-	C	7 00	550	T10	<b>~</b> 1	C	Com	555	7	Cor	ת 7 ת	ui.	
5	GIII	TILL	Ala	Ser	565	PIO	116	Glu	Cys	570	GIII	Arg	Ser	ALG	575	Gru
J	T 011	Dro	Mot	37 - 3		λνα	Cln	qaA	Thr		802	Cvc	Lan	V = l		Gly
	neu	PIO	Mec	580	Giu	Arg	GIII	Asp	585	Аор	Ser	Суз	пеа	590	r y r	GLY
	Gly	Gln	Glm		Tle	T.e.u	ጥh r	Gly		λen	Dhe	ሞh r°	Ser		Ser	Lvs
	Gry	OIII	595	MCC	110	LCu	1111	600	GIII	L'311	FIIC	1111	605	014	001	<i>,</i>
10	Val	Va 1		Thr	Glu	Ivs	Thr	Thr	Δen	Gly	Gln	Gln		Tro	Glu	Met
		610	1110			_,_	615		TIOP	<b>-</b>	<b></b>	620				
	Glu		Thr	Val	Asp	Lvs		Lys	Ser	Gln	Pro		Met	Leu	Phe	Val
	625				-	630	-				635					640
		Ile	Pro	Glu	Tyr	Arq	Asn	Lys	His	Ile	Arq	Thr	Pro	Val	Lys	Val
15					645			_		650	_				655	
	Asn	Phe	Tyr	Val	Ile	Asn	Gly	Lys	Arg	Lys	Arg	Ser	Gln	Pro	Gln	His
				660					665					670		
	Phe	Thr	Tyr	His	Pro	Val	Pro.	Ala	Ile	Lys	Thr	Glu	Pro	Thr	Asp	Glu
			675					680					685			
20	Tyr	Asp	Pro	Thr	Leu	Ile	Cys	Ser	Pro	Thr	His	Gly	Gly	Leu	Gly	Ser
		690					695					700				
		Pro	Tyr	Tyr	Pro		His	Pro	Met	Val		Glu	Ser	Pro	Ser	_
	705					710	_				715				_	720
0.5	Leu	Val	Ala	Thr		Ala	Pro	Cys	Gin		Phe	Arg	Thr	GIY		ser
25		D	7	77.	725	m	~1 m	<b>~</b> 1~	<b>01</b> -	730	Desa	77-	7. l -	17-1	735	Th. 125
	ser	Pro	Asp	740	Arg	ıyı	GIII	Gln	745	ASI	PIO	Ald	HIG	750	neu	TYL
	Gla	7~~	Cor		Car	T.em	Car	Pro		T.AII	Len	G1v	<b>ጥ</b> ኒንም		Gln	Pro
	GIII	Arg	755	цуз	361	пец	Jer	760	Ser	пец	пец	GIY	765	0111	0111	110
30	Ala	Len		Ala	Ala	Pro	Leu	Ser	Leu	Ala	Asp	Ala		Ara	Ser	Val
		770					775					780		_		
	Leu	Val	His	Ala	Gly	Ser	Gln	Gly	Gln	Ser	Ser	Ala	Leu	Leu	His	Pro
	785				_	790		_			795					800
	Ser	Pro	Thr	Asn	Gln	Gln	Ala	Ser	Pro	Val	Ile	His	Tyr	Ser	Pro	Thr
35					805					810					815	
	Asn	Gln	Gln	Leu	Arg	Cys	Gly	Ser	His	Gln	Glu	Phe	Gln	His	Ile	Met
				820					825					830		
	Tyr	Cys	Glu	Asn	Phe	Ala	Pro	Gly	Thr	Thr	Arg	Pro	-	Pro	Pro	Pro
	_		835					840		_			845		<b>_</b>	
40	Val		Gln	Gly	Gln	Arg			Pro	Gly	Ser		Pro	Thr	vaı	Ile
	<b>~</b> 1	850	<b>a</b> 1	3	77-	ml	855					860	7	~1	T)	Dwo
			GIN	Asn	Ата			GIN	Arg	Ата		гув	ASI	GLY	Pro	Pro 880
	865		λαn	Cln	Larg	870		Leu	Dro	ת דת	875	1753	Thr	Tla	Lve	
45	Vai	SET	MSP	GIII	вя5		val	neu	PIO	890		vaı	TIIL	116	895	
40	Glu	Gln	Asn	T.e.i			Thr	ጥህተ	Len			Val	Asn	Glu		Ile
	0.4	V-11	11011	900		01		-1-	905		1100			910		
	Ara	Lvs	Glu			Glv	Pro	Pro			Asn	Gln	Thr			Leu
	5	-,-	915			<b>-</b> -1		920					925			
50	Gln	Ser			Pro	Arq	Ala			Pro	Pro	Val	Ala	Thr	Met	Val
		930				2	935		· L	_		940				
	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	val	Val	Pro	Ile	Leu	Val	Glu
	945	_				950			_		955					960
	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly
55					965					970					975	
	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	' Lys	Lev	ı Thr	: Lev	Lys	Phe	: Ile	: Cys	Thr

				980					985					990				
	Thr (		Lys 995	Leu	Pro	Val		Trp .000	Pro	Thr	Leu		Thr .005		Leu	Thr		
5	Tyr (	Gly 010	Val	Gln	Cys		Ser .015	Arg	Tyr	Pro		His .020	Met	Lys	Gln	His		
	Asp 1	Phe	Phe	Lys		Ala .030	Met	Pro	Glu		Tyr .035	Val	Gln	Glu		Thr .040		
	Ile 1	Phe	Phe				Gly	Asn	_			Arg	Ala					
10	Phe (	Glu				Leu	Val				Glu	Leu	_			Asp		
	Phe 1		Glu		Gly	Asn		Leu		His	Lys		Glu		Asn	Tyr		
	Asn :		075 His	Asn	Val	Tyr		.080 Met	Ala	Asp	Lys		.085 Lys	Asn	Gly	Ile		
15		090	7	Dha	T ***		1095	77 d	3	<b>71</b> 4		100	<b>a</b> 1	0	17-1	<b>71</b> -		
	Lys '	vaı	ASII	Pne		.110	Arg	uis	Asn		115	Asp	GIY	ser		.120		
	Leu I	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr			Gly	Asp	Gly				
20	Leu :	T. 211	Dro		125	wie	T3 12-	Len		1130	<b>01</b> 5	Co	X 3		1135	Taro		
20	neu .	Leu		.140	ASII	urs	TÄT		145	1111	GIII	ser		1150	Ser	цуь		
	Asp 1			Glu	Lys	Arg			Met	Val	Leu			Phe	Val	Thr		
	Ala A		155 Glv	Tle	Thr	Len		Met	Δsn	Glu	T.e.u		1.165 I.ve					
25		170	1				175		р			180	275					
			(2)	TATE	- - -	. T. C. N	. EOF	. cr		NO - 1								
			(2)	TNE	ORMA	TITON	, POP	( SE(	מד ז	NO:1	L34:							
		(i	) SE	QUEN	ICE C	HAR!	CTEF	RIST	cs:									
30					TH:			-	irs									
					E: nu ANDEL				<u>.</u>									
					DLOGY			_										
35		/:	; ) R	401 EC	יו דווי	ጥሊኮ፤	2. ar	227										
33				EATU	CULE JRE:	IIPI	s: Cl	ANC										
					ME/KE CATIO			_	eque	nce								
40					HER I													
		(x	:i) S	EQUE	ENCE	DESC	CRIPT	CION	: SE	Q ID	NO:	134:						
	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	48	
45	Met	Val	Ser	Lys		Glu	Glu	Leu	Phe		Gly	Val	Val	Pro		Leu		
	1				5					10					15			
	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	96	
50	Val	Glu	Leu	-	Gly	Asp	Val	Asn	_	His	Lys	Phe	Ser		Ser	Gly		
50				20					25					30				
	GAG																144	
	Glu	Gly		Gly	Asp	Ala	Thr		Gly	Lys	Leu	Thr		Lys	Phe	Ile		
55			35					40					45					
	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC	ACC	192	
																		269

	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		
5										CGC Arg							240	
10										CCC Pro 90							288	
15										AAC Asn							336	
10										AAC Asn						_	384	
20										CTG Leu	-						432	
25										ATG Met							480	
30										CAC His 170					_		528	
0.5										AAC Asn					Asp		576	
35									Tyr	CTG Leu				Ser			624	
40								Arg		CAC His			Leu				672	
45		Thr					Thr					Glu				TCC Ser 240	720	
50						Gly					Leu					TAC Tyr	768	
					Lys					Arg					a Lei	C ATC	816	
55	GAC	GAG	CTC	GAG	CTO	G GAC	TTC	GAT	CAC	AAC	GAC	C GA	A CTO	TA E	C CA	g AAG	864	270

										_,,							
	Asp	Glu	Leu 275	Glu	Leu	Glu	Leu	Asp 280	Gln	Lys	Asp	Glu	Leu 285	Ile	Gln	Lys	
	CTG	CAG	AAC	GAG	CTG	GAC	AAG	TAC	CGC	TCG	GTG	ATC	CGA	CCA	GCC	ACC	912
5		Gln															
		290					295	_	_			300	_				
		CAG															960
10	305	Gln	Ата	GIN	гÀг	310	ser	Ата	Ser	Thr	ьеи 315	GIn	GIÀ	GLu	Pro	-	
.0	303					310					313					320	
	ACC	AAG	CGG	CAG	GCG	ATC	TCC	GCC	GAG	CCC	ACC	GCC	TTC	GAC	ATC	CAG	1008
	Thr	Lys	Arg	Gln	Ala	Ile	Ser	Ala	Glu	Pro	Thr	Ala	Phe	Asp	Ile	Gln	
					325					330					335		
15	~ n m	ama		~~ m	ama		~~~										
		CTC Leu															1056
	wsh	шеп	SET	340	vai	1111	пеп	PIO	345	TÅT	PIO	гур	Ser	350	GIII	ser	
									J J					330			
20	AAG	GAT	CTT	ATA	AAG	GAA	GCT	ATC	CTT	GAC	AAT	GAC	TTT	ATG	AAG	AAC	1104
	Lys	Asp	Leu	Ile	Lys	Glu	Ala	Ile	Leu	Asp	Asn	Asp	Phe	Met	Lys	Asn	
			355					360					365				
	TITO	GAG	CTC	TTCC	CAC	አጥር	C 3 C	070	7 CC	oma.	a.m	mam	3 m/d	m » «	<b>600</b>	ama	1150
25		Glu															1152
		370			<b></b>		375			vul	тор	380	Nicc	- 7 -	110	V 4 1	
		TAT															1200
20		Tyr	Gly	Lys	Asp		Cys	Ile	Ile	Lys		Gly	Asp	Val	Gly		
30	385					390					395		•			400	
	CTG	GTG	TAT	GTC	ATG	GAA	GAT	GGT	AAG	GTT	GAA	GTT	ACA	AAA	GAA	GGT	1248
		Val															
					405			_	_	410				_	415	-	
35																	
	_	AAG															1296
	vaı	Lys	Leu	420	inr	мет	GIŻ	Pro	425	ьуѕ	Val	Pne	GIY		Leu	Ala	
				720					423					430			
40	ATT	CTT	TAC	AAC	TGT	ACC	CGG	ACA	GCG	ACC	GTC	AAG	ACT	CTT	GTA	AAT	1344
	Ile	Leu	Tyr	Asn	Cys	Thr	Arg	Thr	Ala	Thr	Val	Lys	Thr	Leu	Val	Asn	
			435					440					445				
	CITE TO	70 70 70	ama	maa	000	7 mm	<b>63.00</b>	<b>663</b>	G2.2		maa	~~ `			3.00	3.00	1200
45		AAA Lys															1392
		450	200	***	7124		455	AL 9	OIII	Cys	1 110	460	1111	110	Mee	MCC	
		ACA															1440
		Thr	Gly	Leu	Ile		His	Thr	Glu	Tyr		Glu	Phe	Leu	Lys	Ser	
50	465					470					475					480	
	GTT	CCA	ACA	TTC	CAG	AGC	Стт	רכייי	aas	GAG	אדכ	רידיר	אַמַר	שממ	ידייניי	GCT	1488
		Pro															1400
					485	_	~			490				. 4 =	495		•
55	_																
	GAT	GTC	CTT	GAA	GAG	ACC	CAC	TAT	GAA	AAT	GGA	GAA	TAT	ATT	ATC	AGG	1536
																	2

272

									•	212							
	Asp	Val	Leu	Glu 500	Glu	Thr	His	Tyr	Glu 505	Asn	Gly	Glu	Tyr	Ile 510	Ile	Arg	
5												AGC Ser					1584
10												CCA Pro 540					1632
15												GCC Ala			_	_	1680
.0												GCT Ala					1728
20												GGA Gly					1776
25												AAA Lys				_	1824
30												TCT Ser 620				_	1872
35																CAG Gln 640	1920
33																AAA Lys	1968
40					Asp					Glu					Glu	AAG Lys	2016
45				Gln		_			Asp					Leu		AGA Arg	2064
50			Lys					Leu					Glu			CTA Leu	2112
55		Gly					Ile					g Gly				A GAT Asp 720	2160
	TCI	ACA	ACC	AGA	TTI	TAC	: ACA	GCA	A TGT	r GTC	GTA	A GAA	GC7	TTT	GCC	TAT	2208

										2/3							
	Ser	Thr	Thr	Arg	Phe 725	Tyr	Thr	Ala	Cys	Val 730	Val	Glu	Ala	Phe	Ala 735	Tyr	
5		CAT His															2256
10		CTA Leu															2304
		AAA Lys 770															2352
15		TAT Tyr															2400
20		GAC Asp															2448
25		CCA Pro															2496
30		AGG Arg															2544
25		GCT Ala 850															2592
35		GGG															2640
40		GAG Glu															2688
45		ATA Ile															2736
50		TTC Phe														GGA Gly	2784
55		GAT Asp 930				TAA											2802

274

## (2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 933 amino acids
- (B) TYPE: amino acid

5

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- 10 (v) FRAGMENT TYPE: internal
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

15	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
20	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
25	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly
30	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn
	145					150					155					160
35	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
40	Ser	Lys 210	-	Pro	Asn	Glu	Lys 215	_	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230		Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
45	Gly	Leu	Arg	Ser	Arg 245	Gly	Ser	Met	Gly	Thr 250		Arg	Asp	Leu	Gln 255	
	Ala	Leu	Gln	Glu 260	-	Ile	Glu	Glu	Leu 265	_	Gln	Arg	Asp	Ala 270		Ile
	Asp	Glu	Leu 275	Glu	Leu	Glu	Leu	Asp 280		Lys	Asp	Glu	Leu 285	Ile	Gln	Lys
50	Leu	Gln 290		Glu	Leu	Asp	Lys 295		Arg	Ser	Val	Ile 300		Pro	Ala	Thr
	Gln 305		Ala	Gln	Lys	Gln 310		Ala	Ser	Thr	Leu 315		Gly	Glu	Pro	Arg 320
	Thr	. Lys	Arg	Gln	Ala	Ile	Ser	Ala	Glu	Pro	Thr	Ala	Phe	. Asp		Gln
55				- •	325					330	)				335	_

274

Asp Leu Ser His Val Thr Leu Pro Phe Tyr Pro Lys Ser Pro Gln Ser

				340					345					350		
	Lys	Asp	Leu 355	Ile	Lys	Glu	Ala	Ile 360	Leu	Asp	Asn	Asp	Phe 365	Met	Lys	Asn
5	Leu	Glu 370	Leu	Ser	Gln	Ile	Gln 375	Glu	Ile	Val	Asp	Cys 380	Met	Tyr	Pro	Val
	Glu 385	Tyr	Gly	Lys	Asp	Ser 390	Cys	Ile	Ile	Lys	Glu 395	Gly	Asp	Val	Gly	Ser
	Leu	Val	Tyr	Val	Met 405	Glu	Asp	Gly	Lys	Val 410		Val	Thr	Lys	Glu 415	
10	Val	Lys	Leu	Cys 420		Met	Gly	Pro	Gly 425		Val	Phe	Gly	Glu 430		Ala
	Ile	Leu	Tyr 435	Asn	Cys	Thr	Arg	Thr		Thr	Val	Lys	Thr		Val	Asn
15	Val	Lys 450	Leu	Trp	Ala	Ile	Asp		Gln	Сув	Phe	Gln 460	Thr	Ile	Met	Met
	Arg 465	Thr	Gly	Leu	Ile	Lys 470	His	Thr	Glu	Tyr	Met 475		Phe	Leu	Lys	Ser 480
	Val	Pro	Thr	Phe	Gln 485	Ser	Leu	Pro	Glu	Glu 490		Leu	Ser	Lys	Leu 495	
20	Asp	Val	Leu	Glu 500	Glu	Thr	His	Tyr	Glu 505		Gly	Glu	Tyr	Ile 510		Arg
	Gln	Gly	Ala 515	Arg	Gly	Asp	Thr	Phe 520	Phe	Ile	Ile	Ser	Lys 525		Thr	Val
25	Asn	Val 530	Thr	Arg	Glu	Asp	Ser 535	Pro	Ser	Glu	Asp	Pro 540	Val	Phe	Leu	Arg
	Thr 545	Leu	Gly	Lys	Gly	Asp 550	Trp	Phe	Gly	Glu	Lys 555	Ala	Leu	Gln	Gly	Glu 560
	Asp	Val	Arg	Thr	Ala 565	Asn	Val	Ile	Ala	Ala 570	Glu	Ala	Val	Thr	Cys 575	Leu
30				580					585				Gly	590		
			595					600					Ala 605			
35		610					615					620	Asp			
	625					630					635		Glu			640
					645					650			Ile		655	_
40				660					665				Arg	670		
			675					680					Arg 685			
45		690					695					700	Glu		_	
	705					710					715		Ser			720
E0					725					730			Ala		735	
50				740					745				Pro	750		
			755					760					Phe 765			
55		770					775					780	Cys			
	Glu	ıyr	val	АТА	Pro	Glu	Ile	Ile	Leu	Asn	Lys	Gly	His	Asp	Ile	Ser

276

										2/6							
	785					790					795					800	
		Asp	Tyr	Trp	Ser 805		Gly	Ile	Leu	Met 810		Glu	Leu	Leu	Thr 815		
5	Ser	Pro	Pro	Phe		Gly	Pro	Asp			Lys	Thr	Tyr			Ile	
5	Leu	Arg	Gly 835	820 Ile	Asp	Met	Ile	Glu 840	825 Phe	Pro	Lys	Lys	Ile 845	830 Ala	Lys	Asn	
	Ala			Leu	Ile	Lys	_		Cys	Arg	Asp			Ser	Glu	Arg	
10		850 Gly	Asn	Leu	Lys		855 Gly	Val	Lys	Asp		860 Gln	ГЛS	His	Lys	_	
	865 Phe	Glu	Gly	Phe		870 Trp	Glu	Gly	Leu		875 Lys	Gly	Thr	Leu		880 Pro	
	Pro	Ile	Ile	Pro	885 Ser	Val	Ala	Ser	Pro	890 Thr	Asp	Thr	Ser	Asn	895 Phe	Asp	
15	Ser	Phe		900 Glu	Asp	Asn	Asp	Glu	905 Pro	Pro	Pro	Asp	Asp	910 Asn	Ser	Gly	
	Trp	_	915 Ile	Asp	Phe			920					925				
20		930															
			(2)	) INI	FORM	ATIO	1 FOI	R SE(	) ID	NO:	136:						
		( :		EQUEI LENC													
25				TYP				_	ills								
				STR					2								
			(D)	TOP	orog.	Y: 1:	inea	c									
		(:	ii) l	MOLE	CULE	TYP	E: cl	ANC									
30		(:	ix)	FEAT	JRE:												
				) NAI				_	eque	nce							
				) LO: ) OT:													
35																	
		(:	xi)	SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	136:					
				TTG Leu													48
40				204		_			_					_			
				CAG													96
	Glu	Leu	Arg	Gln 20	Arg	Asp	Ala	Leu	Ile 25	Asp	Glu	Leu	Glu	Leu 30	Glu	Leu	
45																	
				GAC Asp													144
	nap	0111	35	Aup	Giu	ыси	110	40	цуз	Dea	GIII	. Asii	45	пси	vsh	БуЗ	
50	TAC	CGC	TCG	GTG	ATC	CGA	CCA	GCC	ACC	CAG	CAG	GCG	CAG	AAG	CAG	AGC	192
	Tyr	Arg 50	Ser	Val	Ile	Arg	Pro 55	Ala	Thr	Gln	Gln	Ala 60	Gln	Lys	Gln	Ser	
	GCG	AGC	ACC	TTG	CAG	GGC	GAG	CCG	CGC	. Acc	AAG	CGC	CAG	GCG	ATC	TCC	240
55																ser	<del>-</del>
	65					70					75					80	

5						GAT Asp 90						288
J .						AAG Lys						336
10						TTG Leu						384
15						GAG Glu						432
20						CTG Leu						480
25						GTG Val 170						528
						ATT Ile						576
30						GTA Val			_	_		624
35						AGG Arg						672
40						GTT Val						720
45						GAT Asp 250						768
.0						CAA Gln				Asp		816
50					Val				Glu		TCA Ser	864
55				Leu				Lys			TGG Trp	912

E	TTT Phe 305	GGA Gly	GAG Glu	AAA Lys	GCC Ala	TTG Leu 310	CAG Gln	GGG Gly	GAA Glu	GAT Asp	GTG Val 315	AGA Arg	ACA Thr	GCA Ala	Asn	GTA Val 320	960
5				GAA Glu													1008
10	Lys	His	Leu	ATT Ile 340	Gly	Gly	Leu	Asp	Asp 345	Val	Ser	Asn	Lys	Ala 350	Tyr	Glu	1056
15	Asp	Ala	Glu 355	GCT Ala	Lys	Ala	ГÀЗ	Tyr 360	Glu	Ala	Glu	Ala	Ala 365	Phe	Phe	Ala	1104
20	AAC Asn	CTG Leu 370	AAG Lys	CTG Leu	TCT Ser	GAT Asp	TTC Phe 375	AAC Asn	ATC Ile	ATT Ile	GAT Asp	ACC Thr 380	CTT	GGA Gly	GTT Val	GGA Gly	1152
25	GGT Gly 385	TTC Phe	GGA Gly	CGA Arg	GTA Val	GAA Glu 390	CTG Leu	GTC Val	CAG Gln	TTG Leu	AAA Lys 395	AGT Ser	GAA Glu	GAA Glu	TCC Ser	AAA Lys 400	1200
	ACG Thr	TTT Phe	GCA Ala	ATG Met	AAG Lys 405	Ile	CTC Leu	AAG Lys	AAA Lys	CGT Arg 410	His	ATT Ile	GTG Val	GAC Asp	ACA Thr 415	AGA Arg	1248
30	CAG Gln	CAG Gln	GAG Glu	CAC His 420	Ile	CGC Arg	TCA Ser	GAG Glu	AAG Lys 425	Gln	ATC Ile	ATG Met	CAG Gln	GGG Gly 430	GCT Ala	CAT His	1296
35				Ile					Arg					Ser		TAT Tyr	1344
40			Met					Суя					Leu			ATT Ile	1392
45	CTC Leu 465	Arg	GAT Asp	AGA Arg	GGI Gly	TCG Ser 470	Phe	GA/	A GAT 1 As <u>i</u>	TC:	r ACA r Thi 475	Thr	AGA Arg	TTI Phe	TAC Tyr	ACA Thr 480	1440
43	GCA Ala	A TG7 a Cys	GTC Val	GTA L Val	A GAZ L Glu 48	ı Ala	TTT	r GCC	C TAT	r CTC	u Hi	r TCC s Sei	C AAA	A GGF S Gly	A ATO / Ile 495	ATT lle	1488
50	TAC Ty	C AGG	GA(	C CTO p Lev 500	ı Ly	G CCI	A GAZ	A AA' u As:	T CTO n Lev	u Il	C CT	A GA' u Asj	r CAG p Hi:	C CGA S Arg	g Gly	r TAT y Tyr	1536
55	GC(	C AAi a Ly:	A CTO	u Va	r GA l As	T TT	r GG e Gl	C TT y Ph 52	e Al	A AA a Ly	G AA s Ly	A AT. s Il	A GG e Gl	y Ph	r GG e Gl	A AAG y Lys	1584

5	AAA Lys	ACA Thr 530	TGG Trp	ACT Thr	TTT Phe	TGT Cys	GGG Gly 535	ACT Thr	CCA Pro	GAG Glu	TAT Tyr	GTA Val 540	GCC Ala	CCA Pro	GAG Glu	ATC Ile	1632
	ATC Ile 545	CTG Leu	AAC Asn	AAA Lys	GGC Gly	CAT His 550	GAC Asp	ATT Ile	TCA Ser	GCC Ala	GAC Asp 555	TAC Tyr	TGG Trp	TCA Ser	CTG Leu	GGA Gly 560	1680
10	ATC Ile	CTA Leu	ATG Met	TAT Tyr	GAA Glu 565	CTC Leu	CTG Leu	ACT Thr	GGC Gly	AGC Ser 570	CCA Pro	CCT Pro	TTC Phe	TCA Ser	GGC Gly 575	CCA Pro	1728
15	GAT Asp	CCT Pro	ATG Met	AAA Lys 580	ACC Thr	TAT Tyr	AAC Asn	ATC Ile	ATA Ile 585	TTG Leu	AGG Arg	GGG Gly	ATT Ile	GAC Asp 590	ATG Met	ATA Ile	1776
20	GAA Glu	TTT Phe	CCA Pro 595	AAG Lys	AAG Lys	ATT Ile	GCC Ala	AAA Lys 600	AAT Asn	GCT Ala	GCT Ala	AAT Asn	TTA Leu 605	ATT Ile	AAA Lys	AAA Lys	1824
25	CTA Leu	TGC Cys 610	AGG Arg	GAC Asp	AAT Asn	CCA Pro	TCA Ser 615	GAA Glu	AGA Arg	TTA Leu	GGG Gly	AAT Asn 620	TTG Leu	AAA Lys	AAT Asn	GGA Gly	1872
	GTA Val 625	AAA Lys	GAC Asp	ATT Ile	CAA Gln	AAG Lys 630	CAC His	AAA Lys	TGG Trp	TTT Phe	GAG Glu 635	GGC Gly	TTT Phe	AAC Asn	TGG Trp	GAA Glu 640	1920
30	GGC Gly	TTA Leu	AGA Arg	AAA Lys	GGT Gly 645	ACC Thr	TTG Leu	ACA Thr	CCT Pro	CCT Pro 650	ATA Ile	ATA Ile	CCA Pro	AGT Ser	GTT Val 655	GCA Ala	1968
35															AAC Asn		2016
40	GAA Glu	CCA Pro	CCA Pro 675	CCT Pro	GAT Asp	GAC Asp	AAC Asn	TCA Ser 680	GGA Gly	TGG Trp	GAT Asp	ATA Ile	GAC Asp 685	TTC Phe	TCG Ser	GAT Asp	2064
45	CCA Pro	CCG Pro 690	GTC Val	GCC Ala	ACC Thr	ATG Met	GTG Val 695	AGC Ser	AAG Lys	GGC Gly	GAG Glu	GAG Glu 700	CTG Leu	TTC Phe	ACC Thr	GGG Gly	2112
	GTG Val 705	GTG Val	CCC Pro	ATC Ile	CTG Leu	GTC Val 710	GAG Glu	CTG Leu	GAC Asp	GGC Gly	GAC Asp 715	GTA Val	AAC Asn	GGC Gly	CAC His	AAG Lys 720	2160
50	TTC Phe	AGC Ser	GTG Val	TCC Ser	GGC Gly 725	GAG Glu	GGC Gly	GAG Glu	GGC Gly	GAT Asp 730	GCC Ala	ACC Thr	TAC Tyr	GGC Gly	AAG Lys 735	CTG Leu	2208
55	ACC Thr	CTG Leu	AAG Lys	TTC Phe 740	ATC Ile	TGC Cys	ACC Thr	ACC Thr	GGC Gly 745	AAG Lys	CTG Leu	CCC Pro	GTG Val	CCC Pro 750	TGG Trp	CCC Pro	2256

280

5						GGC Gly						2304
J						TTC Phe						2352
10						TTC Phe						2400
15						GAG Glu						2448
20						AAG Lys 825			_		_	2496
25						AGC Ser					_	2544
25						GTG Val						2592
30						GCC Ala			-		_	2640
35						CTG Leu						2688
40	-	-			 	CCC Pro 905	Asn			His	ATG Met	2736
45			Glu			Ala			Gly		GAC Asp	2784
45		Tyr	AA Lys									2799
50												

50

- (2) INFORMATION FOR SEQ ID NO:137:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 932 amino acids
- 55 (B) TYPE: amino acid
  - (C) STRANDEDNESS: single

281

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

```
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:
```

	Met 1	Gly	Thr	Leu	Arg 5	Asp	Leu	Gln	Tyr	Ala 10	Leu	Gln	Glu	Lys	Ile 15	Glu
10	Glu	Leu	Arg	Gln 20	Arg	Asp	Ala	Leu	Ile 25	Asp	Glu	Leu	Glu	Leu 30	Glu	Leu
	Asp	Gln	Lys 35	Asp	Glu	Leu	Ile	Gln 40	Lys	Leu	Gln	Asn	Glu 45	Leu	Asp	Lys
15	Tyr	Arg 50	Ser	Val	Ile	Arg	Pro 55	Ala	Thr	Gln	Gln	Ala 60	Gln	Lys	Gln	Ser
	Ala 65	Ser	Thr	Leu	Gln	Gly 70	Glu	Pro	Arg	Thr	Lys 75	Arg	Gln	Ala	Ile	Ser 80
	Ala	Glu	Pro	Thr	Ala 85	Phe	Asp	Ile	Gln	Asp 90	Leu	Ser	His	Val	Thr 95	Leu
20			Tyr	100					105					110		
			Asp 115					120					125			
25		130	Val	_			135					140	_	_		
	145		Lys			150		_			155	_				160
			Val		165					170					175	
30		_	Lys	180					185					190		
			Thr 195		_			200			_		205			
35	_	210	Cys				215			•		220				
	225		Tyr			230		_			235					240
40			Glu		245		_			250					255	
40	_		Asn	260		_			265		_		_	270		
			11e 275					280					285			
45		290	Glu	-			295		_			300	-	_	_	_
	305	_		_		310		-		_	315	_				Val 320
50					325			_		330					335	
50	_			340					345					350		Glu
			355					360					365			Ala
55		370					375					380				Gly
	Gly	Phe	Gly	Arg	Val	Glu	Leu	Val	Gln	Leu	Lys	Ser	Glu	Glu	Ser	Lys

	385					390					395					400
	Thr	Phe	Ala	Met	Lys 405	Ile	Leu	Lys	Lys	Arg 410	His	Ile	Val	Asp	Thr 415	Arg
5	Gln	Gln	Glu	His 420	Ile	Arg	Ser	Glu	Lys 425	Gln	Ile	Met	Gln	Gly 430	Ala	His
	Ser	Asp	Phe 435	Ile	Val	Arg	Leu	Tyr 440	Arg	Thr	Phe	Lys	Asp 445	Ser	Lys	Tyr
	Leu	Tyr 450	Met	Leu	Met	Glu	Ala 455	Cys	Leu	Gly	Gly	Glu 460	Leu	Trp	Thr	Ile
10	Leu 465	Arg	Asp	Arg	Gly	Ser 470	Phe	Glu	Asp	Ser	Thr 475	Thr	Arg	Phe	Tyr	Thr 480
	Ala	Cys	Val	Val	Glu 485	Ala	Phe	Ala	Tyr	Leu 490	His	Ser	Lys	Gly	Ile 495	Ile
15	Tyr	Arg	Asp	Leu 500	Lys	Pro	Glu	Asn	Leu 505	Ile	Leu	Asp	His	Arg 510	Gly	Tyr
	Ala	Lys	Leu 515	Val	Asp	Phe	Gly	Phe 520	Ala	Lys	Lys	Ile	Gly 525	Phe	Gly	Lys
	Lys	Thr 530	Trp	Thr	Phe	Cys	Gly 535	Thr	Pro	Glu	Tyr	Val 540	Ala	Pro	Glu	Ile
20	545			-	-	550	_				555	_	_		Leu	560
					565					570					Gly 575	
25				580					585			_		590	Met	
			595					600					605		Lys	
		610	_	-			615					620			Asn	
30	625	_	_			630		_	_		635				Trp	640
	_			_	645					650					Val 655	
35				660					665					670	Asn	
			675					680					685		Ser	
		690					695		_	_		700			Thr	
40	705					710					715				His	720
					725					730	•				735	Leu
45				740					745					750		Pro
			755					760	)				765	i		Tyr
	Pro	770		Met	Lys	Gln	His		Phe	Phe	E Lys	Ser 780		Met	Pro	Glu
50	Gly 785	_	· Val	Gln	Glu	Arg 790		: Ile	Phe	Phe	ъуs 795		) Asp	Gly	Asn	Tyr 800
	Lys	Thr	Arg	Ala	Glu 805		Lys	Ph∈	Glu	Gly 810	_	Thr	Lev	ı Val	. Asn 815	Arg
55	Ile	Glu	. Leu	Lys 820		lle	Ası	Phe	E Lys 825		ı Ası	Gly	/ Ası	11e 830		Gly
	His	Lys	: Leu	ເ Glu	ı Tyr	Asn	Ту	c Asr	ı Ser	His	s Ası	ı Val	L Ty	r Ile	e Met	Ala

			835					840					845					
		850					855					860		Arg				
5	Ile 865	Glu	Asp	Gly	Ser	Val 870	Gln	Leu	Ala	Asp	His 875	Tyr	Gln	Gln	Asn	Thr 880		
	Pro	Ile	Gly	Asp	Gly 885	Pro	Val	Leu		Pro 890		Asn	His	Tyr	Leu 895			
	Thr	Gln	Ser	Ala 900		Ser	Lys	Asp			Glu	Lys	Arg	Asp 910		Met		
10	Val	Leu	Leu 915		Phe	Val	Thr	Ala 920		Gly	Ile	Thr		Gly	Met	Asp		
	Glu	Leu 930		Lys				920	·				925					
15		230	(2)	) INI	ZODM?	יייייי	T POI	O CEC	3 TD	NO.	120.							
.0		(-		EQUE						NO:	130:							
		١.	(A)	LENG	GTH:	2184	a bas	se pa										
20			(C)	TYPE STRA	ANDEI	ONES	5: si	ingle	9									
				TOPO														
25				OLEC		TYP	s: CI	AAC										
23				NAN					equei	ıce								٠
				OTE														
30		()	ci) S	EQUI	ENCE	DESC	CRIPT	CION	: SE	O ID	NO:	138:						
														CCC			48	
25	Met 1	vai	Ser	rys	GIY 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu		
35	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	96	
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly		
40														AAG		ATC	144	
	Glu	Gly	Glu 35	Gly	qaA	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile		
														GTG			192	
45	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		
	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG	AAG	240	
50	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys		
	CAG	CAC	GAC	TTC	TTC	AAG	TCC	GCC	ATG	CCC	GAA	GGC	TAC	GTC	CAG	GAG	288	
														Val				
55	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC		GAG	336	
																		283

									•	-0-							
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
5					GGC Gly												384
			TTC		GAG Glu			AAC					AAG		_		432
10		130					135					140					
15	_				CAC His												480
15					AAC Asn 165										_		528
20					GAC Asp												576
25					CCC Pro												624
30					AAC Asn										_	_	672
25					GGG Gly												720
35																GAG Glu	768
40					AAA Lys					Ile					Pro	. CGC Arg	816
45				Leu					Thr					Lys		CGG Arg	864
50			Asp					Glu					Asr			GTG Val	912
		Gln					Lys					Arg				TTC Phe 320	960
55	ATO	: ATC	CGC	TGC	CTG	CAG	TGG	AC(	C ACT	r GTC	TA S	C GA	A CG	C ACC	C TTO	C CAT	1008

285

									2	285							
	Ile	Ile	Arg	Cys	Leu 325	Gln	Trp	Thr	Thr	Val 330	Ile	Glu	Arg	Thr	Phe 335	His	
5				-	GAG Glu												1056
10					CTC Leu												1104
15					AGT Ser												1152
10					AAG Lys												1200
20					AAG Lys 405												1248
25					CGC Arg												1296
30					GAC Asp												1344
35					AGG Arg												1392
33					CGC Arg							Tyr					1440
40					CAC His 485											Arg	1488
45					Gly										Leu	CAC His	1536
50									Asp					Asn		ATG Met	1584
55			Lys					Lys					Gly			AAG Lys	1632
55	GAG	GGG	ATC	AAG	GAC	GGT	. GCC	ACC	ATG	AAG	ACC	TTI	TGC	GGC	ACA	CCT	1680

286

									•	200							
	Glu 545	Gly	Ile	Lys	Asp	Gly 550	Ala	Thr	Met	Lys	Thr 555	Phe	Cys	Gly	Thr	Pro 560	
	GAG	TAC	CTG	GCC	CCC	GAG	GTG	CTG	GAG	GAC	ТАА	GAC	TAC	GGC	CGT	GCA	1728
5		Tyr															
		-			565					570		_	-	_	575		
		GAC															1776
10	vaı	Asp	rrp	580	GIY	ьеu	GIY	vaı	va1 585	Met	Tyr	GIU	Met	Met 590	Cys	GIA	
10				300					505					220			
	CGC	CTG	CCC	TTC	TAC	AAC	CAG	GAC	CAT	GAG	AAG	CTT	TTT	GAG	CTC	ATC	1824
	Arg	Leu	Pro	Phe	Tyr	Asn	Gln	Asp	His	$\operatorname{Glu}$	Lys	Leu	Phe	Glu	Leu	Ile	
			595					600					605				
15	ama	ATG	C X C	~~~	7 M.C	000	mma	aaa	ccc	3 CC	C mm	cam	aaa	C7.C	ccc	እ እ C	1872
																Lys	10/2
	БСИ	610	014	Giu	110	y	615	110	AT 9	****	LCu	620	110			272	
20		TTG															1920
		Leu	Leu	Ser	Gly		Leu	Lys	Lys	Asp		Lys	Gln	Arg	Leu		
	625					630					635					640	
	GGG	GGC	TCC	GAG	GAC	GCC	AAG	GAG	ATC	ATG	CAG	CAT	CGC	TTC	TTT	GCC	1968
25	Gly	Gly	Ser	Glu	Asp	Ala	Lys	Glu	Ile	Met	Gln	His	Arg	Phe	Phe	Ala	
					645					650				•	655		
	aam	3 ma	ama.		a. a	07 G	000	ma	<b>63.</b> 6			ama		003	000	mma	2016
		ATC Ile															2016
30	Cly		V 44 1	660	0111	112.0	val	-7-	665	<i></i> , _	Lys	шси	501	670			
	AAG	CCC	CAG	GTC	ACG	TCG	GAG	ACT	GAC	ACC	AGG	TAT	TTT	GAT	GAG	GAG	2064
	Lys	Pro		Val	Thr	Ser	Glu		Asp	Thr	Arg	Tyr		Asp	Glu	Glu	
35			675					680					685				
33	TTC	ACG	GCC	CAG	ATG	ATC	ACC	ATC	ACA	CCA	CCT	GAC	CAA	GAT	GAC	AGC	2112
																Ser	
		690					695					700					
40																	
40																TCC	2160
	705		Cys	vaı	Asp	710		Arg	Arg	PIC	715		PIO	6111	PHE	Ser 720	
	, 05										, 10					,	
	TAC	TCG	GCC	AGC	AGC	ACG	GCC	TGA									2184
45	Tyr	Ser	Ala	Ser	Ser	Thr	Ala										
					725												
			(2	) IN	FORM	IATIC	N FO	R SE	O II	ONO:	139:	;					
50			,-	,													
		(		_		CHAR											
						727			cids	3							
						minc EDNES			6								
55						Y: 1		_									•
			,			-		-									

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

5		\-	,	J_Q0.		220		LION	· OE	ם בי	140.	137.				
	1				5					10				Pro	15	
				20					25					Val 30		
10			35					40					45	Lys		
		50					55					60		Val		
15	65					70					75			His		80
					85					90				Val	95	
				100					105					Arg 110		
20			115					120					125	Leu		
		130					135					140		Leu		
25	145					150					155			Gln	_	160
					165					170				Asp	175	
20				180					185					Gly 190	_	-
30			195					200					205	Ser		
		210					215					220		Leu		
35	225					230					235			Tyr	_	240
					245					250				Val	255	
40				260					265					Arg 270		_
40			275					280					285	Lys		
		290					295					300		Phe		
45	305					310					315			Asn		320
					325					330				Thr	335	
E0				340					345					Ile 350		
50			355					360					365	qsA		_
		370					375					380		Glu		
55	385					390					395			Glu		400
	гÀг	Leu	Leu	G1y	Lys	Gly	Thr	Phe	Gly	Lys	Val	Ile	Leu	Val	Lys	Glu

288

										288						
					405					410					415	
	Lys	Ala	Thr	Gly 420	Arg	Tyr	Tyr	Ala	Met 425	Lys	Ile	Leu	Lys	Lys 430	Glu	Val
_	Ile	Val			Asp	Glu	Val			Thr	Leu	Thr			Arg	Val
5	<b>*</b>	<b>~</b> 1	435		•	TT.1 =		440			- 1		445	MD	<b>~</b>	D1
	Leu	450	Asn	ser	Arg	HIS	455	Pne	Leu	Thr	Ala	ьеи 460	гуѕ	ıyr	ser	pne
	Gln 465	Thr	His	Asp	Arg	Leu 470	Суѕ	Phe	Val	Met	Glu 475	Tyr	Ala	Asn	Gly	Gly 480
10		Leu	Phe	Phe	His 485	Leu	Ser	Arg	Glu	Arg 490	Val	Phe	Ser	Glu	Asp 495	Arg
	Ala	Arg	Phe	Tyr 500		Ala	Glu	Ile	Val 505		Ala	Leu	Asp	Tyr 510		His
45	Ser	Glu	-		Val	Val	Tyr	_		Leu	Lys	Leu		_	Leu	Met
15	Leu	Asp	515 Lvs	Asp	Gly	His	Ile	520 Lvs	Ile	Thr	Asp	Phe	525 Glv	Leu	Cys	Lys
		530	•	•	•		535	-				540	•		•	•
	Glu 545	Gly	Ile	Lys	qaA	Gly 550	Ala	Thr	Met	Lys	Thr 555	Phe	Cys	Gly	Thr	Pro 560
20		Tyr	Leu	Ala	Pro		Val	Leu	Glu	Asp	Asn	Asp	Tyr	Gly	Arg	
					565					570					575	
	Val	Asp	Trp	Trp 580	Gly	Leu	Gly	Val	Val 585	Met	Tyr	Glu	Met	Met 590	Cys	Gly
25	Arg	Leu	Pro 595	Phe	Tyr	Asn	Gln	Asp 600	His	Glu	Lys	Leu	Phe 605	Glu	Leu	Ile
	Leu	Met 610	Glu	Glu	Ile	Arg	Phe 615	Pro	Arg	Thr	Leu	Gly 620	Pro	Glu	Ala	Lys
	Ser		Leu	Ser	Gly	Leu		Lys	Lys	Asp	Pro		Gln	Arg	Leu	Gly
	625			_		630					635					640
30	Gly	Gly	Ser	Glu	Asp 645	Ala	Lys	Glu	Ile	Met 650	Gln	His	Arg	Phe	Phe 655	Ala
	Gly	Ile	Val	Trp 660	Gln	His	Val	Tyr	Glu 665	_	Lys	Leu	Ser	Pro 670	Pro	Phe
35	Lys	Pro	Gln 675	Val	Thr	Ser	Glu	Thr 680		Thr	Arg	Tyr	Phe 685	Asp	Glu	Glu
00	Phe		Ala	Gln	Met	Ile				Pro	Pro			Asp	Asp	Ser
	Met	690 Glu		Val	Asp	Ser	695 Glu	Ara	Ara	Pro	His	700 Phe	Pro	Gln	Phe	Ser
	705	014	Cyb		ı.sp	710	014	my	n. g	110	715		110	<b></b>		720
40	Tyr	Ser	Ala	Ser	Ser 725	Thr	Ala									
			(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	140:					
AE		,	٠, ~	~~~		~173 <b>~</b>	1 am=	<b>.</b>	7.00							
45		(	•					RIST se p								
				DEN					GILE	1						

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

50 (ii) MOLECULE TYPE: cDNA

- (ix) FEATURE:
- (IX) FEATURE
  - (A) NAME/KEY: Coding Sequence
- (B) LOCATION: 1...2391
  - (D) OTHER INFORMATION:

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

5															CAG Gln 15		48
10															GGC Gly		96
15															CCA Pro		144
	_														ATC Ile		192
20															AAG Lys		240
25															TGC Cys 95		288
30															CAC His		336
35															GAG Glu		384
															GTT Val		432
40															CTC Leu		480
45															CTG Leu 175		528
50															ACT Thr		576
55															CTC Leu		624
	GGG	GAT	GAG	ATC	TTC	CTA	CTG	TGT	GAC	AAG	GTG	CAG	AAA	GAG	GAC	ATT	672

290

									•	290							
	Gly	Asp 210	Glu	Ile	Phe	Leu	Leu 215	Cys	Asp	Lys	Val	Gln 220	Lys	Glu	Asp	Ile	
5			TAT Tyr														720
10			GAT Asp														768
45			GAC Asp														816
15			CCT Pro 275														864
20			GAT Asp														912
25			GAG Glu														960
30			GAC Asp														1008
25			GCT Ala														1056
35			CTG Leu 355														1104
40			GGG Gly					Ala									1152
45		Val					Pro					Ala				GTA Val 400	1200
50						Ala					Pro					GGC Gly	1248
EE					Val					Pro					Ala	GGG Gly	1296
55	GAA	GGA	ACG	CTG	TCA	GAG	GCC	CTC	CTC	CAC	CTC	CAC	TTI	GA1	GA	GAA	1344

									•	291							
	Glu	Gly	Thr 435	Leu	Ser	Glu	Ala	Leu 440	Leu	Gln	Leu	Gln	Phe 445	Asp	Asp	Glu	
5									AGC Ser					_	_	_	1392
10		-							GAG Glu								1440
15									ACT Thr								1488
10									ACA Thr 505								1536
20									CCG Pro								1584
25		-							ATT Ile							_	1632
30									GAT Asp								1680
35									GGG								1728
									AAG Lys 585						_	_	1776
40									CTG Leu								1824
45								Trp	CCC Pro				Thr				1872
50		Gly					Ser		TAC			His					1920
55						Ala			GAA Glu		туг					Thr	1968
	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	: AAG	ACC	CGC	GCC	GAG	GTG	AAG	2016

										292							
	Ile	Phe	Phe	Lys 660	Asp	Asp	Gly	Asn	Tyr 665	Lys	Thr	Arg	Ala	Glu 670	Val	Lys	
5	TTC Phe	GAG Glu	GGC Gly 675	GAC Asp	ACC Thr	CTG Leu	GTG Val	AAC Asn 680	CGC Arg	ATC Ile	GAG Glu	CTG Leu	AAG Lys 685	GGC Gly	ATC Ile	GAC Asp	2064
10		AAG Lys 690															2112
45		AGC Ser															2160
15	AAG Lys	GTG Val	AAC Asn	TTC Phe	AAG Lys 725	ATC Ile	CGC Arg	CAC His	AAC Asn	ATC Ile 730	GAG Glu	GAC Asp	GGC	AGC Ser	GTG Val 735	CAG Gln	2208
20	CTC Leu	GCC Ala	GAC Asp	CAC His 740	Tyr	CAG Gln	CAG Gln	AAC Asn	ACC Thr 745	Pro	ATC Ile	GGC Gly	GAC Asp	GGC Gly 750	Pro	GTG Val	2256
25	CTG Leu	CTG Leu	CCC Pro 755	Asp	AAC Asn	CAC His	TAC Tyr	CTG Leu 760	Ser	ACC Thr	CAG Gln	TCC Ser	GCC Ala 765	Leu	AGC Ser	AAA Lys	2304
30	GAC Asp	CCC Pro 770	Asn	GAG Glu	AAG Lys	CGC Arg	GAT Asp 775	His	ATG Met	GTC Val	CTG Lev	CTG Leu 780	Gli	TTC	GTG Val	ACC Thr	2352
35		GCC Ala					Gly					туг			Λ	•	2394
			(2	!) IN	IFORM	IATIC	N FC	R SI	EQ II	NO:	:141	:					
40		(	(i) S (A) (B) (C)	EQUE LEI TYI STI	ENCE IGTH: PE: & RANDI	CHAF 797 amino	RACTE ami aci	ERIST ino a id sing:	rics acid:	:							
45			(v) 1	MOL1 FRAGI	MENT	TYP	E: i	nter	nal								
				SEQ													
50	1				5					10					15	n Ala y Met	
			=	20					25					30		o Gly	
55			35					40	ı				45	5		e Asn	2

		50					55					60				
	65					Gly 70					75					80
5					85	His				90					95	
	Asp	Gly	Phe	Tyr 100	Glu	Ala	Glu	Leu	Cys 105	Pro	Asp	Arg	Cys	Ile 110	His	Ser
			115			Ile		120			-		125			
10		130				Ile	135					140				
	145					Gly 150					155			_		160
15					165	Arg				170					175	
				180		Pro			185					190		
			195			Arg		200					205			
20		210				Leu	215					220				
	225					Gly 230					235		_			240
25					245	Arg				250					255	
				260		Leu			265		_			270		
•			275			Arg		280					285			
30		290				Asp	295					300				
	305					Lys 310					315					320
35					325	Pro				330					335	
				340		Pro			345					350		
40			355			Ile		360					365			
40		370				Ser	375					380				
	385					Ala 390					395					400
45					405	Ala				410					415	
				420		Ala			425					430		
			435			Glu		440					445			
50		450				Leu	455					460				
	465					Asp 470					475					480
55					485	Pro				490					495	
	Pro	GLU	Ala	тте	ınr	Arg	Leu	Va1	Thr	Glv	Ala	Gln	Ara	Pro	Pro	Asn

294

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500
                                      505
      Pro Ala Pro Ala Pro Leu Gly Ala Pro Gly Leu Pro Asn Gly Leu Leu
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      Ser Gly Asp Glu Asp Phe Ser Ser Ile Ala Asp Met Asp Phe Ser Ala
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                             535
                                                  540
      Leu Leu Ser Gln Ile Ser Ser Leu Asp Pro Pro Val Ala Thr Met Val
                          550
                                              555
      Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu
                      565
                                          570
10
      Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly
                                      585
      Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr
                                  600
      Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr
15
                              615
      Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His
                          630
      Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr
                                          650
20
      Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu Val Lys
                                      665
      Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly Ile Asp
                                  680
                                                      685
      Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyx
25
                             695
      Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile
                          710
                                              715
      Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln
                      725
                                          730
30
     Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val
                                      745
     Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys
                                  760
     Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr
35
                             775
      Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys
                          790
               (2) INFORMATION FOR SEQ ID NO:142:
40
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2394 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
45
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
            (ix) FEATURE:
50
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2391
               (D) OTHER INFORMATION:
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:
55
     ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG
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294

295

										295							
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
5							GTA Val										96
10							ACC Thr										144
15							CCC Pro 55	-			-						192
13							TGC Cys										240
20							TCC Ser							_	_		288
25							GAC Asp										336
30							ACC Thr										384
35							GGC Gly 135								_		432
33		_														AAC Asn 160	480
40							AAG Lys									AGC Ser	528
45										Asn						GGC Gly	576
50									Tyr					Ser		CTG Leu	624
E÷			Asp					Arg					Leu			TTC Phe	672
55	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TCC	720

									4	290							
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240	
5									GAA Glu								768
10									CCC Pro 265								816
15									CGC Arg								864
									AGC Ser								912
20									ACA Thr								960
25									CAC His								1008
30									TTC Phe 345								1056
35									AAC Asn								1104
									AGT Ser								1152
40									GAG Glu								1200
45						Cys			GTG Val							Gly	1248
50															Asp	AAT Asn	1296
55				Asn										Asn		AAC Asn	1344
	TCT	GGC	AGC	TGC	CTC	GGT	GGG	GAT	GAG	ATC	TTC	CTA	CTG	TGT	GAC	: AAG	1392

297

									•	291							
	Ser	Gly 450	Ser	Cys	Leu	Gly	Gly 455	Asp	Glu	Ile	Phe	Leu 460	Leu	Cys	Asp	Lys	
5		CAG Gln															1440
10		CGA Arg															1488
		TTC Phe														_	1536
15		GTC Val															1584
20		ATG Met 530															1632
25		GAG Glu															1680
30		AGT Ser															1728
25		GCT Ala													_		1776
35		CCC Pro															1824
40		CCC Pro 610															1872
45		GCC Ala										Ala				_	1920
50		GCT Ala				Val					Gln					Val	1968
		GTC Val			Pro					Ala					Ala		2016
55	AAG	CCC	ACC	CAG	GCT	GGG	GAA	. GGA	ACG	CTG	TCA	A GAG	GCC	CTG	CTG	CAG	2064

									•	290							
· .	Lys	Pro	Thr 675	Gln	Ala	Gly	Glu	Gly 680	Thr	Leu	Ser	Glu	Ala 685	Leu	Leu	Gln	
5 .										GCC Ala							2112
10										TCC Ser		-					2160
15										GTG Val 730							2208
13										ATA Ile							2256
20										GCT Ala							2304
25										GAA Glu							2352
30										CAG Gln	,			TAA			2394
			(2)	) IN	FORM	ATIOI	v FO	R SE	Q ID	NO:	143:						
35		(:	(B)	LENO TYP	GTH: E: an	797 mino	ACTE ami acie S: s:	no a d	cids								
40			(D) ii)   v)   F	MOLE	CULE	TYP	-	rote									
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	1				5					10					15	Leu	
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		50	Thr				55	Val				60				Thr	
55	65					70					75					Lys 80 Glu	•
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										200						
					85					90					95	
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110		Glu
5	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120		Asn	Arg	Ile	Glu 125		Lys	Gly
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	145					150					155	Asp				160
10					165					170		Ile			175	
				180					185			Pro		190		
15			195					200				Thr	205			
		210					215					Val 220				
20	225					230					235	Glu				240
20					245					250		Pro			255	
				260					265			Glu		270		
25			275					280				Cys Thr	285			
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30	305					310					315	His				320
					325					330		Ala			335	
				340					345			Ile		350		
35			355					360				Ile	365			
		370					375					380 Gly				
40	385					390					395	Arg				400
					405					410		Pro			415	
				420					425			Arg		430		
45			435					440				Leu	445			
		450					455					460 Gly				
50	465 Ala	Arg	Gly	Ser	Phe	470 Ser	Gln	Ala	Asp	Val	475 His	Arg	Gln	Val	Ala	480 Ile
				Thr	485					490		Leu			495	
EE	Arg	Val		500 Met	Gln	Leu	Arg		505 Pro	Ser	Asp	Arg		510 Leu	Ser	Glu
55	Pro	Met	515 Glu	Phe	Gln	Tyr	Leu	520 Pro	Asp	Thr	Asp	Asp	525 Arg	His	Arg	Ile

		530					535					540				
	545				Lys	550					555					560
5	Lys	Ser	Pro	Phe	Ser 565	Gly	Pro	Thr	Asp	Pro 570	Arg	Pro	Pro	Pro	Arg 575	Arg
	Ile	Ala	Val	Pro 580	Ser	Arg	Ser	Ser	Ala 585	Ser	Val	Pro	Lys	Pro 590	Ala	Pro
	Gln	Pro	Tyr 595	Pro	Phe	Thr	Ser	Ser 600	Leu	Ser	Thr	Ile	Asn 605	Tyr	Asp	Glu
10	Phe	Pro 610	Thr	Met	Val	Phe	Pro 615	Ser	Gly	Gln	Ile	Ser 620	Gln	Ala	Ser	Ala
	Leu 625	Ala	Pro	Ala	Pro	Pro 630	Gln	Val	Leu	Pro	Gln 635	Ala	Pro	Ala	Pro	Ala 640
15	Pro	Ala	Pro	Ala	Met 645	Val	Ser	Ala	Leu	Ala 650	Gln	Ala	Pro	Ala	Pro 655	Val
	Pro	Val	Leu	Ala 660	Pro	Gly	Pro	Pro	Gln 665	Ala	Val	Ala	Pro	Pro 670	Ala	Pro
	Lys	Pro	Thr 675	Gln	Ala	Gly	Glu	Gly 680	Thr	Leu	Ser	Glu	Ala 685		Leu	Gln
20	Leu	Gln 690	Phe	Asp	Asp	Glu	Asp 695	Leu	Gly	Ala	Leu	Leu 700		Asn	Ser	Thr
	Asp 705	Pro	Ala	Val	Phe	Thr 710	Asp	Leu	Ala	Ser	Val 715	Asp	Asn	Ser	Glu	Phe 720
25	Gln	Gln	Leu	Leu	Asn 725	Gln	Gly	Ile	Pro	Val 730	Ala	Pro	His	Thr	Thr 735	Glu
	Pro	Met	Leu	Met 740	Glu	Tyr	Pro	Glu	Ala 745	Ile	Thr	Arg	Leu	Val 750	Thr	Gly
	Ala	Gln	Arg 755	Pro	Pro	Asp	Pro	Ala 760	Pro	Ala	Pro	Leu	Gly 765		Pro	Gly
30	Leu	Pro 770	Asn	Gly	Leu	Leu	Ser 775	Gly	Asp	Glu	Asp	Phe 780		Ser	Ile	Ala
	Asp 785	Met	Asp	Phe	Ser	Ala 790	Leu	Leu	Ser	Gln	Ile 795	Ser	Ser			

## **CLAIMS**

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- 1. A method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution to the degree of the influence on the cellular response.
- 2. A method according to claim 1, as used for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway, or part thereof, the method comprising recording the result of the influence on mechanically intact living cell or cells, as manifested in spatially distributed light emitted from a luminophore which is present in the cell or cells and which is capable of being redistributed, by modulation of the pathway, in a manner which is related to the redistribution of the at least one component of the intracellular pathway, processing the recorded result to provide quantitative information about the spatially distributed light and correlating the quantitative information to the degree of the influence on the intracellular pathway.
  - 3. A method according to claim 1 or 2, wherein the quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence.
- 4. A method according to any of the preceding claims, wherein the influence is contact between the mechanically intact living cell or the group of mechanically intact living cells with a

chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance.

- 5. A method according to claim 4 wherein the substance is a substance whose effect on anintracellular pathway is to be determined.
  - 6. A method according to any of the preceding claims, wherein the recording is made at a single point in time after the application of the influence.
- 7. A method according to any of claims 1-5, wherein the recording is made at two points in time, one point being before, and the other point being after the application of the influence.
  - 8. A method according to any of claims 1-5, wherein the recording is performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes.

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- 9. A method according to any of claims 1-7, wherein the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.
- 10. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence.

- 11. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of associating with a component which is capable of being redistributed in manner which is physiologically relevant to the degree of the influence.
- 12. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is experimentally determined to be correlated to the degree of the influence.
- 13. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed, by modulation of the intracellular pathway, in substantially the same manner as the at least one component of the intracellular pathway.
- 14. A method according to any of claims 1-13, wherein the luminophore is a luminophore which is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a decrease in the intensity of the luminescence.
- 15. A method according to any of claims 1-13, wherein the variation or result with respect to the spatially distributed light emitted by the luminophore is detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway, and one of which undergoes redistribution in response to the influence, thereby changing the amount of resonance energy transfer, the change in the resonance energy transfer being measured as a change in the intensity of emission from the luminophore.
  - 16. A method according to claim 15, wherein the change in the intensity of the emission from the luminophore is sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion

17. A method according to any of claims 1-16, wherein the property of the light being recorded is intensity, fluorescence lifetime, polarization, wavelength shift, or other property which is modulated as a result of the underlying cellular response.

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18. A method according to any of claims 1-15 or 17, wherein the recording of the spatially distributed light is performed using a recording system which records the spatial distribution of a recordable property of the light in the form of an ordered array of values.

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19. A method according to claim 18, wherein the recording of the spatial distribution of the recordable property of the light is performed using a charge transfer device such as a CCD array or a vacuum tube device such as a vidicon tube.

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20. A method according to any of the preceding claims, wherein the light to be measured passes through a filter which selects the desired component of the light to be measured and rejects other components.

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- 21. A method according to any of the preceding claims, wherein the recording of the spatial distribution of the recordable property of light is performed by fluorescence microscopy.
- 22. A method according to any of the preceding claims, wherein the recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures.

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23. A method according to any of claims 2-22, wherein the intracellular pathway is an intracellular signalling pathway.

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- 24. A method according to any of the preceding claims, wherein the luminophore is a fluorophore.
- 5 25. A method according to any of the preceding claims wherein the luminophore is a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells.
- 26. A method according to any of the preceding claims, wherein the luminophore is a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.
- 27. A method according to claim 26, wherein the luminescent polypeptide is a GFP as defined herein.
  - 28. A method according to claim 27 wherein the GFP is selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein.
- 29. A method according to claim 28 wherein the GFP is a GFP variant selected from the group consisting of F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP.
  - 30. A method according to any of the previous claims for detecting intracellular translocation of a biologically active polypeptide affecting intracellular processes upon activation, the method comprising
    - a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a GFP which is N- or C-terminally tagged, optionally through a linker, to a biologically active polypeptide under conditions permitting expression of the nucleotide sequence,

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- b) modulating the activity of the biologically active polypeptide by incubating the cell or cells with a substance having biological activity and
- c) measuring the fluorescence produced by the incubated cell or cells and determining the result or variation with respect to the fluorescence, such result or variation being indicative of the translocation of a biologically active polypeptide in said cell.
- 31. A method according to claim 30, wherein the nucleotide sequence is a DNA sequence.
- 32. A method according to claim 30 or 31, wherein the modulation is an activation.
- 33. A method according to claim 30 or 31, wherein the modulation is a deactivation.
- 34. A method according to any of claims 30-33 wherein the fluorescence of the cell or cells is measured prior to the modulation, and the result or variation determined in step (c) is a change in fluorescence compared to the fluorescence measured prior to the modulation.
  - 35. A method according to any of claims 30-34, wherein the intracellular processes are intracellular signalling pathways.
- 36. A method according to claim 34, wherein the change in fluorescence measured in step (c) comprises determining a change in the spatial distribution of the fluorescence.
- 37. A method according to any of the preceding claims wherein the mechanically intact living cell or cells is/are a mammalian cell/mammalian cells which, during the time peroid over which the influence is observed, is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C.

- 38. A method according to any of the preceding claims, wherein the at least one mechanically intact living cell is part of a matrix of identical or non-identical cells.
- 39. A method according to any of claims 1-36 and 38, wherein the cell or cells is/are selected from the group consisting of fungal cells, such as a yeast cell; invertebrate cells including insect cells; and vertebrate cells, such as mammalian cells.
- 40. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, with the proviso that the construct is not a construct coding for a fusion polypeptide in which the biologically active polypeptide is selected from the group consisting of PKC-alpha, PKC-gamma, and PKC-epsilon.
- 41. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and an F64L mutant of GFP.
  - 42. A nucleic acid construct according to claim 40 or 41, wherein the biologically active polypeptide is a protein kinase or a phosphatase.

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- 43. A nucleic acid construct according to any of claims 40-42 wherein the GFP is N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- 44. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a transcription factor or a part thereof which changes cellular localisation upon activation.

- 45. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
- 46. A nucleic acid construct according to any of claims 40-43, wherein the biologically active polypeptide is a protein kinase or a part thereof which changes cellular localisation upon activation.
- 47. A nucleic acid construct according to claim 46, wherein the protein kinase is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - 48. A nucleic acid construct according to claim 46, wherein the protein kinase is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - 49. A nucleic acid construct according to claim 46, wherein the protein kinase is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- 50. A nucleic acid construct according to claim 46, wherein the protein kinase is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 51. A nucleic acid construct according to claim 50 which codes for a PKAc-F64L-S65T-GFP fusion.
  - 52. A nucleic acid construct according to claim 46, wherein the protein kinase is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

53. A nucleic acid construct according to claim 46, wherein the protein kinase is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

- 54. A nucleic acid construct according to claim 46, wherein the protein kinase is a mitogenactivated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 55. A nucleic acid construct according to claim 54, which codes for an ERK1-F64L-S65T-GFP fusion.
  - 56. A nucleic acid construct according to claim 54, which codes for an EGFP-ERK1 fusion.
- 57. A nucleic acid construct according to claim 46, wherein the protein kinase is a cyclindependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 58. A nucleic acid construct according to claim 42 or 43, wherein the biologically active polypeptide is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.
  - 59. A nucleic acid construct according to any of claims 40-58 which is a DNA construct.
- 60. A nucleic acid construct according to any of claims 40-59 wherein the gene encoding GFP is derived from Aequorea victoria.
  - 61. A nucleic acid construct according to claim 60 in which the gene encoding GFP is the gene encoding EGFP as defined herein.

62. A nucleic acid construct according to claim 60 in which the gene encoding a GFP is a gene encoding a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.

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- 63. A DNA construct according to claim 59 and 61 or, where applicable, 62, which is a construct as identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, and 142, or is a variant thereof capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, as defined herein.
- 64. A cell containing a nucleic acid construct according to any of claims 40-63 and capable of expressing the sequence encoded by the construct.

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- 65. A cell according to claim 64, which is a eukaryotic cell.
- 66. A cell according to claim 64, which is selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells, including insect cells, and vertebrate cells, such as mammalian cells.
  - 67. A cell according to claim 66, which is a mammalian cell.
- 68. An organism carrying in at least one of its component cells a nucleic acid sequence as contained in the constructs according to any of claims 40-59, said cell being capable of expressing said nucleic acid sequence.
  - 69. An organism according to claim 68 which is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

- 70. A fluorescent probe comprising a GFP which is N- or C-terminally tagged, optionally via a peptide linker, to a biologically active polypeptide or a part or a subunit thereof which is a component of a intracellular signalling pathway as defined herein, the probe being a probe which is encoded by the nucleic acid construct according to any of claims 40-59.
- 71. A method according to any of claims 1-39, wherein the luminophore is a fusion polypeptide as encoded by the nucleic acid construct according to any of claims 40-63.
- 10 72. A method according to any of claims 1-39 or 71 in which the method of the invention is used in a screening program as defined herein.
  - 73. An apparatus for measuring the distribution of fluorescence in at least one cell, and thereby any change in the distribution of fluorescence in at least one cell, which includes the following component parts: (a) a light source, (b) a means for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a means for rapidly blocking or pass ing the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

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- 74. An apparatus according to claim 73 in which some or all of the system is automated.
- 75. An apparatus according to claim 73 in which components d and e comprise a fluorescence microscope.

- 76. An apparatus according to claim 73 in which component f is a CCD camera.
- 77. An apparatus according to claim 73 in which the image is formed and recorded by an optical scanning system.

- 78. An apparatus according to claim 73 in which a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance.
- 79. An apparatus according to claim 78 in which the liquid addition system is under the control of the computer or electronic system.
  - 80. A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically active substance as defined herein that directly or indirectly affects an intracellular signalling pathway and is potentially useful as a medicament, wherein the result of the individual measurement of each substance being screened which indicates its potential biological activity is based on measurement of the redistribution of spatially resolved luminescence in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.

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- 81 A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway, wherein the result of the individual measurement of each substance being screened which indicates its potential biologically toxic activity is based on measurement of the redistribution of said fluorescent probe in living cells and which undergoes a change in distribution upon activation of an intracellular signal-ling pathway.
- 82. A method according to any of claims 1-80 wherein a fluorescent probe is used in backtracking of signal transduction pathways as defined herein.

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- 83. A method of treating a condition or disease related to the intracellular function of a protein kinase comprising administering to a patient suffering from said condition or disease an effective amount of a compound which has been discovered by any method according to the invention.
- 84. A compound that modulates a component of an intracellular pathway as defined herein, as determined by a method according to the method of the invention.
- 10 85. A medical composition comprising a therapeutic amount of a compound identified according the method of the invention.
  - 86. A method of selectively treating a patient suffering from an ailment which responds to medical treatment comprising obtaining a primary cell or cells from said patient, transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of medicaments suspected of being capable of alleviating said ailment, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting a medicament(s) based on desired activity and acceptable level of side effects and administering an effective amount of said medicament(s) to said patient.
- 87. A method according to any of claims 1-80 of identifying a drug target among the group of biologically active polypeptides which are components of intracellular signalling pathways.

Fig 1

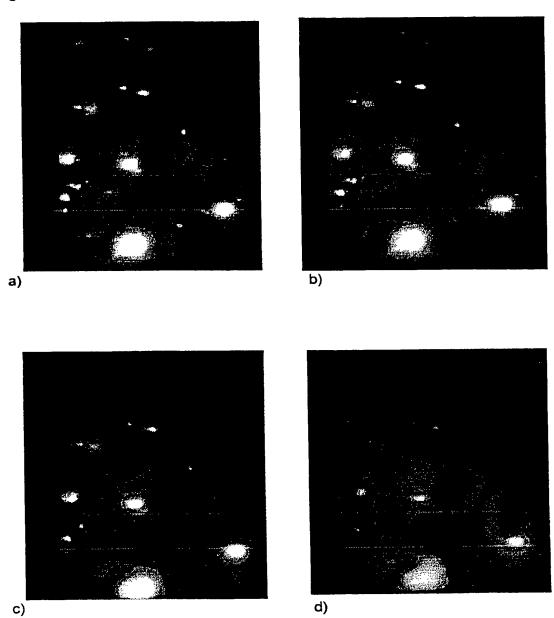


Fig 2

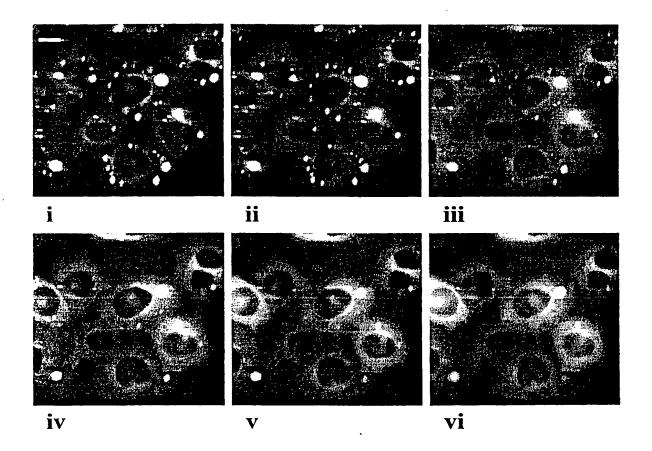
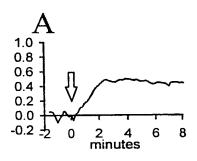
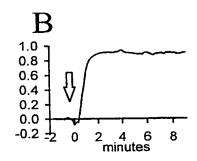
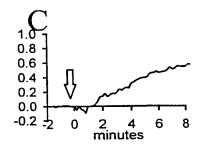
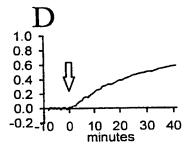


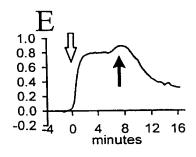
Fig 3

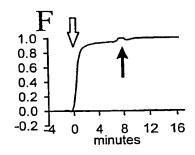


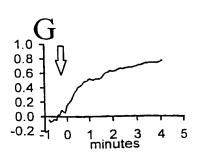














4/12

Fig 4

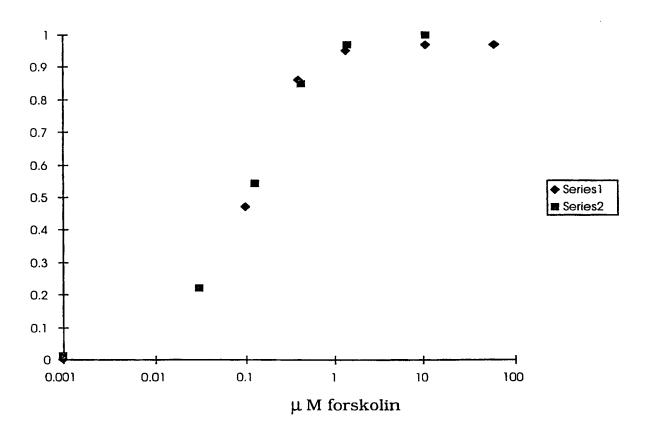


Fig 5

[forskolin]µM	$t_{1/2\text{max}}/s$	t <sub>max</sub> /s				
1	115±21	310±31				
10	69±14	224±47				
50	47±10	125±28				

Fig 6

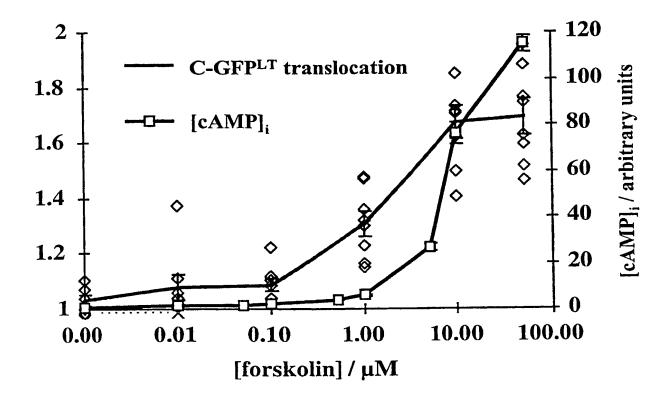
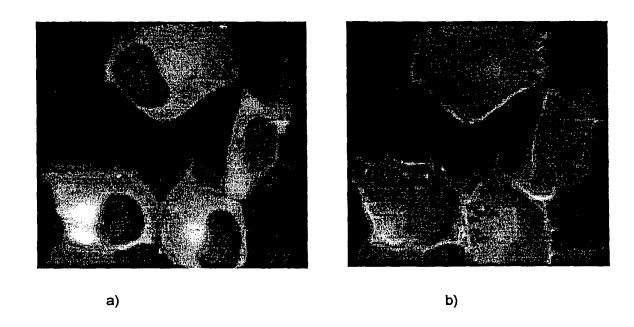


Fig 7



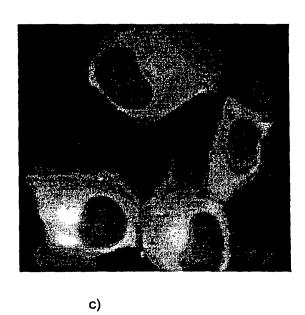
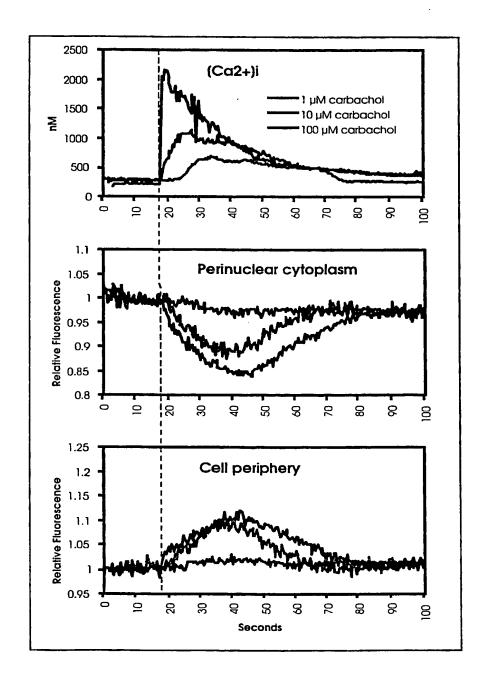
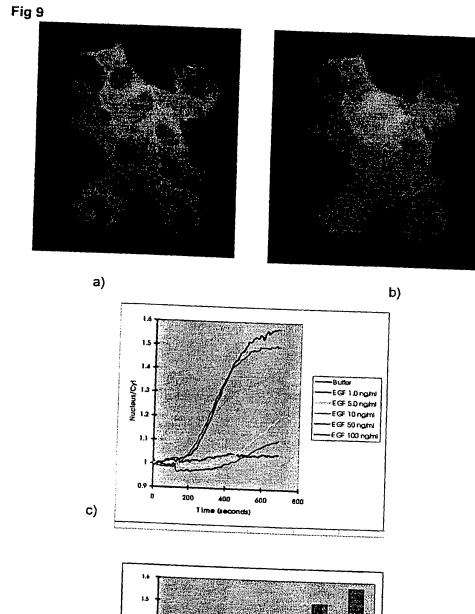
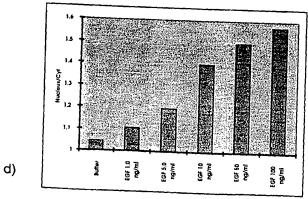


Fig 8





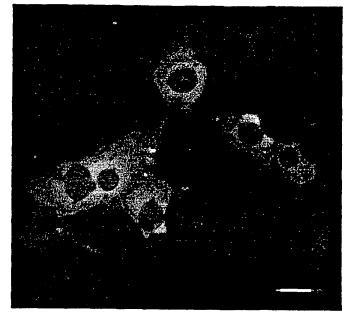


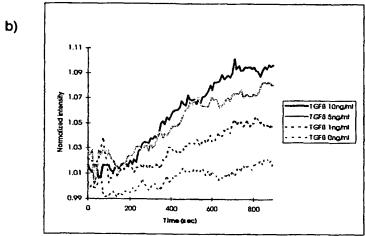


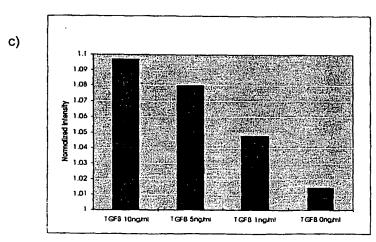






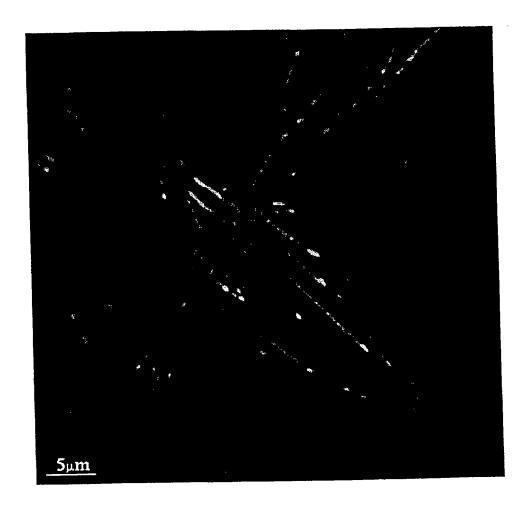






11/12

Fig 11



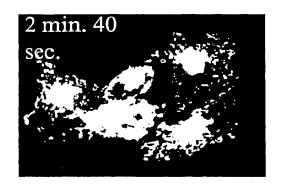
WO 98/45704 PCT/DK98/00145

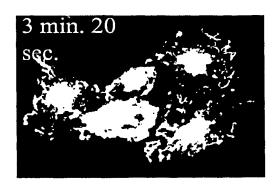
12 / 12

Fig. 12













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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup>: G01N 33/50, C12Q 1/48, 1/25

(11) International Publication Number:

WO 98/45704

(43) International Publication Date:

15 October 1998 (15.10.98)

(21) International Application Number:

PCT/DK98/00145

A3

(22) International Filing Date:

7 April 1998 (07.04.98)

(30) Priority Data:

0392/97

7 April 1997 (07.04.97)

DK

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- (74) Common Representative: NOVO NORDISK A/S; attn. Lars Kellberg, Novo Allé, DK-2880 Bagsværd (DK).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

#### Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:

22 April 1999 (22.04.99)

(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

#### (57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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Int. .tional Application No PCT/DK 98/00145

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 G01N33/50 C120 G01N33/50 C12Q1/48 C12Q1/25 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) GOIN C12Q C12N C07K Documentation searched other than minimum documentation to the extent that such documents are included in the tields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category 3 Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X WO 97 11094 A (NOVONORDISK AS ; THASTRUP 1-27 OLE (DK); TULLIN SOEREN (DK); POULSEN LAR) 30-4027 March 1997 44-60, 64-82,88 see the whole document Υ see claims 28,29, 41,61-63 χ WO 91 01305 A (UNIV WALES MEDICINE) 1-27.7 February 1991 30 - 4042-60, 64-84, 87,88 see page 4, line 15 - line 20 Υ see claims 28,29, 41,61-63 see examples 1-10 Further documents are fisted in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents: T later document published after the international filing date or priority date and not in conflict with the application but "A" document defining the general state of the lart which is not cited to understand the principle or theory underlying the considered to be of particular relevance invention "E" earlier document but published on or after the international X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another involve an inventive step when the document is taken alone document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the document is combined with one or more other, such docu-"O" document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled in the art. document published prior to the international filing date but later than the priority date claimed in ament member of the same patent family Date of the actual completion of the international search Sate of mailing of the international search report **75**, 02, 1999 19 January 1999 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL · 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Hoekstra, S Fax: (+31-70) 340-3016

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see page 8-17	42,43, 46,47
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Bxt	Observations where certain laims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1 X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. X	Although claims 83-84 and claim 87 relate to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy).  Claims Nos.:  85,86 because they relate to parts of the International Application that do not comply with the prescribed requirements to such
	an extent that no meaningful International Search can be carried out, specifically:
	see FURTHER INFORMATION sheet PCT/ISA/210
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box ii	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	ernational Searching Authority found multiple inventions in this international application, as follows:
	see additional sheet
1. X	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
	No consisted additional access for a year timely said books and it and Community this later, the I Complete Danset is
<b>*</b> · L	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark	on Protest  X The additional search fees were accompanied by the applicant's protest.
	No protest accompanied the payment of additional search fees.
	The process accompanies the payment of additional season lees,

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210
Claims Nos.: 85,86
The subject-matter (compounds per se) is solely characterised in claims 85 and 86 by the result to be achieved, no support of a technical character is derivable from the description for the technical formulation of the subject of the search, accordingly no scope of a search could be defined and a meaningfull search is hence not possible.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 47, 49, 53-57

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being serine/threonine protein kinases

2. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 48

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to tyrosine kinases

3. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 50, 51

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to cAMP dependent protein kinases.

4. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 52

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being cGMP dependent protein kinases

5. Claims: Partially: 1-43, 59-82 and 88; Entirely: 58

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being protein phosphatases

6. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 44

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to transcription factors

7. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 45

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to proteins associated with the cytoskeletal network

Information on patent family members

In. Jational Application No PCT/DK 98/00145

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